January 31, 2003

MEMORANDUM

SUBJECT: Atrazine: Response to Public Comments on the EPA's April 16, 2002 Revised Human Health Risk Assessment and Associated Documents for the Reregistration Eligibility Decision (RED). PC Code: 080803. DP Barcode: 284707.

FROM: Catherine Eiden, Branch Senior Scientist
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THROUGH: Donna Davis, Branch Chief
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TO: Kimberly Lowe, Chemical Review Manager
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Please find attached the response document to public comments on the EPA's April 16, 2002, "Atrazine: HED's Revised Human Health Risk Assessment (and Associated Documents) for the Reregistration Eligibility Decision (RED). HED responders included: Catherine Eiden, Vicki Dellarco, Jerry Blondell, and Linda Taylor.

Executive Summary

This memorandum contains HED's responses to public comments submitted during the 60-day public comment period for "Atrazine. HED's Revised Human Health Risk Assessment, April 16, 2002". The HED received 11 sets of comments from academia,, and groups representing the agribusiness and the farming community and their consultants, non-profit organizations, state agencies, and water quality trade associations.

HED received comments from the American Farm Bureau Federation, Triazine Network, and the Louisiana Farm Bureau Federation.

The HED also received comments from 3 non-profit organizations (environmental groups) representing public concerns: the Natural Resources Defense Council (NRDC), Beyond Pesticides/NCAMP, and People for the Ethical Treatment of Animals (PETA).

HED received comments from the State of New York, Office of the Attorney General, the California Department of Pesticide Regulation, and the State of Connecticut, Office of the Attorney General.

From the water quality community, HED received comments from the American Water Works Association (AWWA). From the general public, HED received comments from John Wargo of Yale University.

<u>Agricultural Community Comments</u>

Louisiana Farm Bureau Federation (LFBF):

<u>Comment</u>
LFBF provided comment on the ongoing efforts to manage pesticides in the Iberville, Jefferson Parish, and Thibodaux watersheds to minimize the impacts of atrazine on water quality. Cooperative agreements among state agencies, university programs, and grower groups are cited as providing the best framework to address local water quality issues posed by agriculture. Water quality monitoring is cited as providing proof that cooperative local efforts to change use rates

and use best management practices (BMPs) have reduced the detections and levels of atrazine in the managed areas. The LFBF notes that soil erosion is reduced and soil conservation efforts enhanced as a result of the use of atrazine in the watersheds. In summary, the LFBF supports the continued use of atrazine and local management of water quality impairment, and expresses an interest that EPA review available water monitoring data and produce a timely reregistration decision for atrazine.

<u>HED Response</u>
HED fully supports the idea of cooperative efforts involving local organizations in areas with impaired water quality as a result of atrazine use. HED understands that local responses can be the best approach to solving a localized problem. HED has reviewed the available water monitoring data, and notes that in finished drinking water concentrations of atrazine and the chlorinated degradates tended to be below the MCL of 3 ppb in Jefferson Parish and did not exceed levels of concern. They were also low with the exception of a few spikes in May and June of some years in the Thibodaux CWS, but did not exceed levels of concern. However, the community water system (CWS) at Iberville has exceeded levels of concern for atrazine and the chlorinated degradates as recently as 2001. This CWS has been targeted for mitigation. The situation at the Iberville CWS is an indication that there are CWS impaired by atrazine use even under good management and BMPs that need additional mitigation.

American Farm Bureau Federation (AFBF):

<u>Comment</u>
AFBF provided comment on atrazine's great importance to agriculture. It is an inexpensive, reliable, and effective weed control preferred by farmers, particularly, those growing corn, sorghum, and sugarcane. It is a critical piece of "no-till" or conservation tillage practices in agriculture that helps to reduce soil erosion. Regarding science and the risk assessment, AFBF reiterates the designation of atrazine as "not likely to be carcinogenic to humans". Regarding the toxic effects of atrazine, AFBF states, "Both epidemiological studies of the population in areas where atrazine has been manufactured or used for 40 years and long-term dietary studies using laboratory animals, show that atrazine does not cause adverse effects to reproductive systems, affect genetic development, cause birth defects, affect chromosome structure or disrupt endocrine function, (i.e., is not estrogenic)". Regarding spray drift, AFBF makes the case that atrazine is non-volatile and not subject to drift concerns. As to drinking water concerns, AFBF states that atrazine is found in some water supplies at very low levels, rarely above the MCL of 3 ppb, and that short-term Health Advisory Levels (HALs) have not been exceeded. AFBF notes that through local management detected levels of atrazine have decreased by 60% between 1989 and 1998 in Midwestern streams according to the USGS. Finally, AFBF notes that atrazine is not

found in foods we eat.

<u>HED Response</u>
HED acknowledges the importance of atrazine in agriculture as currently practiced. HED concurs with AFBF's designation of atrazine as not likely to be a human carcinogen. This position is reflected in the human health risk assessment.

Regarding AFBF's statement as to atrazine's toxicity, HED disagrees with AFBF's statements and concludes somewhat differently in the risk assessment that atrazine does have reproductive consequences and does alter endocrine function in test animals and is therefore likely to do so in humans. Short- and intermediate-term exposures to atrazine caused fetal "resorptions" (abortions) in rabbits and delays in pubertal development of young rats, as well as, alterations in the estrus cycle of adult rats by decreasing the luteinizing hormone surge, which affects ovulation (both a reproductive and an endocrine effect). HED believes the results of the animal tests indicate that atrazine and the chlorinated degradates have the potential to disrupt endocrine function and have adverse developmental and reproductive consequences in humans. These toxic effects form the basis of the risk assessment.

HED has received comments that there is evidence that atrazine is present in rainwater and volatilization may be a source of exposure. This may be occurring via volatilization from lakes, rivers, and bays where atrazine is present in dissolved form. HED concludes in the risk assessment that exposure to atrazine in foods humans eat is minimal and not a significant exposure pathway. HED agrees that atrazine is a non-volatile pesticide. HED does not consider volatilization and spray drift to be major contributors to exposure to atrazine in the risk assessment. Even so, HED did conduct inhalation exposure assessments for atrazine as a routine part of the occupational and residential risk assessments.

HED does not completely agree with the statement that atrazine is found in some water supplies at very low levels, rarely above the MCL. HED concluded that atrazine is widely detected in the nation's streams, rivers, and lakes mostly at low levels. This is supported by USGS monitoring programs. However, to date, HED has reviewed large volumes of data on atrazine and the chlorinated degradates in finished drinking water and determined there are 197 CWS with annual average concentrations of atrazine greater than or equal to the MCL of 3.0 ppb. Most of these CWS use surface waters. These CWS represent ~ 2% of CWS in the US using surface water. This occurrence of atrazine above the MCL may not be considered frequent given the number of CWS using surface water in the US (~10,000), but it should not be considered rare, either.

HED defers to the Environmental Fate and Effects Division (EFED) to discuss the decreasing trend of atrazine in Midwestern streams.

Triazine Network:

Comment

The Triazine Network submitted comments on the cancer classification of atrazine, the toxicologic endpoints selected for use in the human health risk assessment, and on the 10-fold FQPA safety factor applied to dietary risk assessments for atrazine. Specifically, the commenter agrees with the classification of atrazine as “not likely to be a human carcinogen”, as stated in the risk assessment. They do disagree with the selection of the 1.8 mg/kg/day endpoint based on disturbances in the luteinizing hormone (LH) surge in adult female rats as the basis of risk assessments for infants and children, and the application of this endpoint in intermediate-term risk assessments. They also note that the endpoint comes from a non-guideline study and this practice should not become routine. It is suggested that an endpoint from a rat 90-day (subchronic) study be used to assess intermediate-term risks. They also disagree with the retention of the 10-fold FQPA safety factor based on increased sensitivity in the young. Specifically, they argue that the decision was driven by data on DACT, and that guideline studies in the young have not produced a NOAEL lower than 1.8 mg/kg/day. The comment concludes that the assessment uses an “ultra conservative” approach.

HED Response

Endpoint selection: The endpoint selected for use in intermediate-term and chronic risk assessment comes from a 6-month study designed to elucidate the potential mechanism of mammary tumor formation in the female Sprague-Dawley rat. As indicated, the study was not a guideline study; however, the endpoint reflects the general mechanism by which atrazine toxicity is believed to function, i.e., disruption of the neuroendocrine system. It also represents the lowest (i.e., most conservative and protective) endpoint in the toxicity database. In this sense, although the study from which the endpoint was taken was not a guideline study, it nevertheless was determined to be the most relevant study for atrazine's toxic mode of action. Available guideline studies did not measure the hormonal parameters necessary to determine endocrine effects.

Regarding the use of the endpoint for both chronic and intermediate-term risk assessments, as stated, the attenuation of the LH surge is deemed to be indicative of atrazine's general toxic mode of action on the neuroendocrine system. A six-month study is generally considered adequate for use in selecting a subchronic endpoint for evaluation of intermediate-term exposures. In the case of atrazine, because attenuation of the LH surge is deemed to be a critical event in the mode of action of atrazine-associated carcinogenesis in the Sprague-Dawley strain of rat, and because a LH surge study of longer duration may be of limited value given that the attenuation of LH surge occurs in normally aging Sprague-Dawley rats around 9 months of age, the 6-month study was selected as the basis for estimating risks associated with both intermediate-term and chronic exposures. An additional safety factor to account for a study duration of less than 12 months was not deemed necessary since attenuation of LH surge occurs in normally aging Sprague-Dawley rats around 9 months of age.

As to the application of this endpoint to risk assessments for infants and children, though this specific endpoint (LH surge attenuation and estrous cycle disruption) is directly applicable only to females 13-50, HED's HIARC noted that this dose is the lowest NOAEL available in the toxicology database (i.e., the most sensitive endpoint), and therefore would be protective of other adverse effects, including those occurring in males, infants and children. Further, the attenuation of the LH surge is considered a biomarker indicative of atrazine's ability to alter hypothalamic-pituitary function in general. Therefore, a separate endpoint was not selected for other populations (i.e., males, infants and children). As discussed in the Scientific Advisory Panel (SAP) report (SAP Report No. 2000-05; Atrazine: Hazard and Dose Response Assessment and Characterization)..... "Because of the rapid developmental brain changes...the influence of Atrazine on neurotransmitters in the hypothalamus and on GnRH may well have a differential, permanent effect on children. This phenomenon is the basis of the relatively new field of behavioral teratology. Atrazine could influence the migration of cells and the connectivity of the CNS. The influence of Atrazine on the hypothalamus and on GnRH may have a differential effect on children. This effect could be latent, and emerge later during the challenge of puberty, or during senescence. Behavioral alterations may be the most sensitive outcome. This possibility should be addressed...." (see Part A, http://www.epa.gov/scipoly/sap/2000/june27/finalparta_atz.pdf and Part B, http://www.epa.gov/scipoly/sap/2000/june27/finalpartb_atz.pdf).

This dose and endpoint replaces the previous dose and endpoint of 3.5 mg/kg/day based on decreased body weight gain and food consumption in a two-year rat bioassay selected by HIARC in 1998. The dose of 1.8 mg/kg/day for use in risk assessment would be protective of effects that occur at the higher dose of 3.5 mg/kg/day as well as protective of effects such as LH surge attenuation and estrous cycle alterations, and any effects that may be associated with alteration of these parameters such as prostatitis in developing males (as seen from pubertal assays on rats).

This endpoint was considered particularly appropriate for assessing intermediate-term and chronic exposures to atrazine in drinking water (the main exposure route of atrazine), as these exposures occur both as seasonal pulses from weeks to months in duration, and chronically from months to years in duration, reflective of atrazine’s use patterns and occurrence in drinking water.

An endpoint of 3.3 mg/kg/day from a subchronic, oral, rat study was considered, but deemed inappropriate because the effect elicited (reduced body weight gain) is not reflective of the general toxic mode of action of atrazine, i.e., in that study there was no assessment of endocrine disruption via hormonal measurements.

FQPA Safety Factor: The decision reflected in the April 16, 2002 human health risk assessment to retain the 10X FQPA safety factor was not based solely on toxicity considerations, nor on a rabbit developmental study using DACT. The decision captured in the document dated April 8, 2002, Atrazine/DACT - Reassessment Report of the FQPA Safety Factor Committee, establishes that residual uncertainties regarding atrazine’s effects on the developing young, and evidence of increased *qualitative* susceptibility from the rabbit developmental study using atrazine were noted. The rabbit developmental study showed increased resorptions of fetuses (abortions) at the same dose of atrazine in which the mother experienced clinical signs and reduced body weight gain. The more severe effect on the young developing fetuses (death) is considered qualitative evidence of the young’s increased sensitivity to atrazine. In addition, the committee found that there were residual concerns and uncertainties regarding the extent of short-and intermediate-term exposure to atrazine in drinking water. Together, these two sources of residual uncertainty led the committee to retain the 10X safety factor for dietary assessments, only. The committee decided that a 3X safety factor was adequately protective of residential exposures. The complete rationale for the FQPA decisions is contained in the FQPA memorandum cited above available on EPA's website: http://www.epa.gov/oppsrrd1/reregistration/atrazine/.

The comment indicates that only the developmental rat study with DACT was considered in the FQPA decision. The comment states that there is no evidence that the developmental study using DACT shows quantitative susceptibility in the young. HED reassessed this study based on similar comments received during the 60-day public comment period on the revised preliminary risk assessment, and concluded that there was no evidence of quantitative susceptibility in the young in the DACT developmental study. HED concurs with the comment and has revised the FQPA memorandum and toxicology chapter and risk assessment accordingly. Maternal and fetal or offspring effects occur at the same doses (25 mg/kg/day). During this reassessment, the entire toxicity database was thoroughly reexamined and the resulting conclusions captured in the April 5th and 8th, 2002 HIARC and FQPA documents, respectively, both available on the previously cited website. That reexamination determined there was no evidence of quantitative susceptibility, but there was evidence of "qualitative" susceptibility in the rabbit developmental study using atrazine (not DACT) based on a weight-of-the-evidence approach using the entire database. This increased qualitative susceptibility is based on reduced body weight gain in the mother versus fetal resorptions (abortion/death) in the pups at equivalent doses.

Regarding comments on sensitivity in the young and the lack of any indication of sensitivity in the young from available guideline studies, the comment states that all evidence indicates that young rats are less sensitive to the neuroendocrine effects caused by atrazine than adult rats. The basis for this conclusion stems from their comparison of the NOAEL/LOAEL from studies on the young animal [those where the young were not directly dosed, two pubertal assays and two recent studies in which young rats were dosed directly] with findings in the available database on the adult animal.

Although the NOAELs in some of the adult studies are lower than those in the young, this apparent difference between the age groups may be attributed to dose spacing or to a difference in dosing duration. For example, comparison of the 28-day LH surge study in the female adult rat [NOAEL of 5 mg/kg/day; LOAEL of 40 mg/kg/day] with the published pubertal study in the female young rat [delayed vaginal opening (VO) NOAEL of 25 mg/kg/day ; LOAEL of 50 mg/kg/day] shows rather similar LOAELs [40 *vs* 50] for similar durations of dosing [young female 20 days]. If the dose-spacing in the adult study were similar to that in the pubertal study [2X], the NOAELs might have been similar also [20 *vs* 25]. In comparisons made by Syngenta, the 6-month study duration far exceeds any study performed in the young animal, and it is well known that lower doses are required to produce an effect following long-duration exposure than for a short-duration exposure. A comparison of the adult NOAELs/LOAELs obtained in the 6-month [1.8/3.65 mg/kg/day] and 28-day [5/40 mg/kg/day] studies illustrates this also.

Based on one of the recent Syngenta studies [described above] in which immature female rats were dosed directly [21-24 days], the lowest NOAEL was 10 mg/kg/day, based on effects [delayed vaginal opening and reduced uterine weight] at 30 mg/kg/day. Comparison of this study with the NOAEL observed in the adult female 28-day LH surge study [NOAEL = 5/mg/kg/day; LOAEL = 40 mg/kg/day] also does not support the conclusion that the young female rat is less sensitive than the adult female rat.

Finally regarding speculation about atrazine's effects in the developing young throughout critical periods of development and the use of non-guideline studies in assessing atrazine, HED notes that endocrine disruption is now considered the main toxic mode of action of atrazine. Residual uncertainties remain at this time regarding that mode of toxic action, and the timing of exposure in the available database. Guideline studies currently used by OPP do not address endocrine disruption, and as a result HED responsibly selected endpoints from non-guideline studies that did assess changes in hormonal parameters. The Agency has established the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to develop the kinds of studies needed to assess neuroendocrine disruption. In the future, atrazine may be subject to further testing along these lines. In the interim, uncertainty regarding atrazine's full effects on the endocrine systems of adults and the young, and the consequences of those effects must be considered. HED acknowledges that because of these remaining toxicity and exposure uncertainties, the human health risk assessment for atrazine and its chlorinated degradates is conservative.

<u>Environmental Community Comments</u>

Natural Resources Defense Council (NRDC):

The Natural Resources Defense Council (NRDC) submitted comments covering a wide range of issues covering drinking water exposures, flaws in interpretation of toxicity data regarding endpoint selection for risk assessment and cancer classification of atrazine, the FQPA safety factor, farm children's and worker exposures, high-end exposures, use of human data, percent-crop-treated information and anticipated residues, and inclusion of exposure through showering in the aggregate risk assessment.

Drinking Water Issues -

<u>Comment</u>
EPA has ignored the MCL in its risk assessment for atrazine. The use of the concentration figure of 12.5 ppb as a safe upper limit in drinking water is wholly unwarranted. EPA has underestimated drinking water exposures.

<u>HED Response</u>

The MCL of 3 ppb is an annual average concentration of atrazine alone that is based on a NOAEL of 0.5 mg/kg/day, a 1000-fold safety factor, and assumes that exposure through drinking water will occupy only 20% of the reference dose. In the case of most pesticides OW assumes that exposure through food may contribute up to 80% of the exposure. In the case of atrazine, however, dietary exposure through food is minimal, and occupies <1% of the reference dose. HED's assessment quantifies and takes into account the dietary exposure to chlorotriazines through food in its aggregate exposure assessment rather than relying on assumptions about dietary exposure. Additionally, the 12.5 ppb DWLOC that OPP has identified is for total chlorotriazines and a 90-day rolling average concentration in contrast to an annual average concentration for atrazine alone. Selection of a 90-day average value was determined to be the most appropriate value to capture seasonal exposures to atrazine.

NRDC discusses the endpoint from a toxicity study considered the basis of the MCL for atrazine. HED's risk assessment was based on a toxic effect and endpoint different from the MCL. The MCL is based on several studies, one of which is a 2-generation reproduction study in rats. The endpoint from the 2-generation reproduction study in rats is reduced body weight gain. On 9/28/92 the OPP (HED RfD Peer Review Committee) in conjunction with representatives of the Office of Water (OW) conducted a review of that study and determined that the endpoint was not statistically significant, and that the NOAEL from that study should be ~ 3.5 mg/kg/day, not the 0.5 mg/kg/day currently reflected in the MCL. This decision was confirmed by the Agency Workgroup on 12/16/92. OPP has worked closely with the Office of Water (OW) while developing the risk assessment for atrazine. OW has indicated that they will review the MCL for atrazine once EPA has completed its risk assessment.

The volume of toxicity data on atrazine indicates that the most relevant toxic endpoints for risk assessment should reflect atrazine's disruption of the neuroendocrine system as its main toxic mode of action. The concentration used in the screening-level assessment as an upper limit of atrazine and its chlorinated degradates, 12.5 ppb, is based on attenuation of the LH surge (disruption of the estrus cycle) a biomarker for its toxic mode of action. It is based on a NOAEL of 1.8 mg/kg/day, which translates to a reference dose (RfD) of 0.018 mg/kg/day reflecting the traditional 100X safety factor, and a population adjusted dose of 0.0018 mg/kg/day reflecting the additional 10X FQPA safety factor. The 10X FQPA safety factor reflects a 3X safety factor for residual uncertainties regarding atrazine's potential effects on childrens' development, and a 3X safety factor for residual uncertainties regarding limitations on the drinking water database. The residual uncertainties identified by the FQPA Committee included limited monitoring data on the degradates and the infrequency of monitoring under the SDWA at specific CWS. It represents the average seasonal concentration over a 90-day period of chlorotriazines that an infant, 1 year old weighing 7 kg and consuming 1 liter of water per day, may safely consume in drinking water as a part of its aggregate exposure to the chlorotriazines through its diet (i.e., exposure through food and water).

It should also be noted that the 12.5 ppb figure was used to screen for CWS with potential exposures of concern. Once identified through the screening process, probabilistic assessments for specific CWS were conducted. The toxic endpoint used as the basis for these probabilistic assessments was the same as that used to calculate the 12.5 ppb figure. However, HED does not intend the 12.5 ppb figure to serve as a standard but as a screening tool. It should be noted that the 12.5 ppb figure is based on an endpoint considered representative of atrazine's main toxic mode of action (neuroendocrine system effects); it is the lowest/most protective endpoint in the toxicity database, and it comes from a sub chronic study well-suited to assessing risks associated with seasonal peaks of chlorotriazines in drinking water as the typical high-end exposures to atrazine occur shortly after application in the Spring.

For those specific CWS undergoing or preparing to undergo intensive monitoring, residual uncertainties regarding the extent and magnitude of exposure to chlorotriazines have been removed, therefore supporting a reduction in the FQPA safety factor to 3X. Based on the availability of reliable drinking water exposure data, HED has recalculated the DWLOC (drinking water level of concern) using a total risk assessment 300-fold uncertainty factor for those CWS currently undergoing or targeted for future intensive monitoring. For these CWS, the DWLOC for a 90-day average concentration of total chlorotriazines becomes 37.5 ppb based on an endpoint of 1.8 mg/kg/day, and a 300-fold uncertainty factor reflecting a 10-fold factor for interspecies variation, a 10-fold factor for intraspecies variability, and a 3-fold safety factor. The remaining 3-fold safety factor reflects residual uncertainties associated with atrazine's toxic effects on the developing child only. For CWS without intensive monitoring as described above, the screening level DWLOC remains 12.5 ppb for total chlorotriazines.

EPA believes that we have not underestimated drinking water exposures in our current assessment. The Environmental Fate and Effects Division's drinking water assessment estimates that ~ 1 million people are exposed to annual average concentrations of atrazine above the MCL of 3 ppb. Based on all available compliance monitoring data and voluntary monitoring on atrazine in finished drinking water through 2001, there are ~ 200 community water systems (CWS) with annual average concentrations of atrazine above 3 ppb. The available monitoring data used in the risk assessment cover ~ 99% of all atrazine use in the US and represent ~ 4000 CWS using surface water collecting data on atrazine.

In the US, there are ~ 55, 000 CWS regulated under the Safe Drinking Water Act (SDWA). Of these 55,000 CWS, 10,000 use surface water and the remaining 45,000 use groundwater. These 200 CWS with levels of atrazine above the MCL use surface water and represent variously 0.036 % of all the CWS, and 2% of the ~ 10,000 CWS using surface water. HED believes that these 200 CWS represent the high-end of atrazine exposure in US drinking water supplies.

Based on the human health risk assessment and analysis of compliance monitoring data from an additional 10 states with atrazine use not included in the April 16, 2002 human health risk assessment, but submitted subsequently to the public release of the assessment, ~ 230,000 to 240,000 individuals are served by 34 CWS identified as having aggregate risk estimates of concern for infants. Altogether, the data set provides information on ~ 4000 CWS with data on atrazine monitored under the SDWA representing 99% of the atrazine use in the US. The US Bureau of Census estimates that 1.4% of the US population is infants < 1 year old. Some of these CWS also have risks of concern for children and adults. Although not precise as to the exact number of individual infants, children, or adults exposed, the assessment does provide for an estimate of the magnitude of the population of concern.

An additional ~50 CWS are estimated as having potential risks of concern. The ~ 50 CWS with the potential for risks of concern were not identified via MCL violations of an annual average of > 3ppb, but the 50 were identified as having a single maximum concentration of $\geq$12.5 ppb. NRDC points out that there may be a hole in industry's methodology for identifying CWS of concern. It may be that an annual average of 3 ppb is too high to identify CWS with 90-day average concentrations in excess of 12.5 ppb, and a lower "trigger" value is needed. To address this issue, HED and EFED considered available data from SDWA compliance monitoring and came to agreement with the registrant on a trigger value of 2.6 ppb based on an annual average concentration in finished water which is considered predictive of the likelihood that a 90-day average during peak use season would exceed the screening DWLOC of 12.5 ppb. CWS identified in the future with potential high-end seasonal exposures based on the annual average trigger of 2.6 ppb will receive intensive monitoring under the Memorandum of Agreement between OPP and the registrant. It should be noted that the annual average trigger of 2.6 ppb is for total chlorotriazines. Therefore, all SDWA compliance monitoring data must first be transformed from a value representing atrazine alone, to a concentration which reflects inclusion of degradates of concern using the appropriate seasonal regression equations described in the April 16, 2002 risk assessment document.

HED believes that these 34 represent CWS with high-end exposures, but not all of them. An annual average concentration value for atrazine close to the current MCL (i.e., the 2.6 ppb total chlorotriazine trigger value) is a plausible indicator of seasonal exposures of concern. In this way, the MCL and the 12.5 ppb figure may work together constructively to identify CWS with seasonal exposures of potential concern.

HED examined data for ~ 4000 CWS using surface water in ~ 31 states representing 99% of atrazine use in the US. Although there are ~ 10,000 CWS using surface water in the US, not all of them collect data on atrazine. Under the SDWA, CWS may apply for waivers if atrazine is not used in the area and/or if compliance monitoring for 3 consecutive quarters shows no detections of atrazine. HED has assumed that these other CWS have received data waivers under the SDWA. Compliance monitoring for the SDWA is under the purview of EPA's OW. OPP has advised OW of NRDC's concern and must defer to OW on the issue of under reporting MCL violations.

Toxicity Issues -

Comment NRDC believes that 1.8 mg/kg bw per day is the lowest observable adverse effect level (LOAEL) rather than the no observable adverse effect level (NOAEL) for suppression of the LH surge in the 6 month LH study and its NOAEL

HED Response EPA's position is that 1.8 mg/kg bw per day is a NOAEL in the 6 month LH surge study by Syngenta. EPA believes it is justified in using 3.6 mg/kg bw per day as a LOAEL for this endpoint. The rationale for the selection of 3.6 mg/kg bw per day as a LOAEL and 1.8 mg/kg bw per day as a NOAEL for suppression of the LH surge is based on a weight of evidence argument. There is a dose response trend for suppression of the LH surge. While the 3.6 mg/kg bw per day dose does not represent a statistically significant decrease in the amount of LH, the dose response trend is supported by the statistically significant difference in vaginal cycling at 3.6 mg/kg bw per day. Vaginal cycling data tends to be less variable than LH data. Thus, EPA acknowledges that selection of 1.8 mg/kg bw per day as a NOAEL for LH suppression is conservative, but errs on the side of health protection. Although there is one statistically significant response for suppression of the LH surge in the 1.8 mg/kg bw per day dose group for one time point, this is not sufficient evidence to designate 1.8 mg/kg bw per day as a LOAEL, particularly in light of the fact there were no statistically significant differences found for vaginal cycling at this dose.

Cancer Issues:

Comment
NRDC believes that carcinogenicity to humans must be reconsidered and "new data" supporting an alternative mode of action and "new data" on carcinogenicity must be included in the weight of evidence determination.

HED Response
It is to be noted that no new data were submitted by NRDC. Additionally, the alternative modes of action discussed by NRDC were considered and discussed previously, both by the Agency and by the FIFRA Scientific Advisory Panel [SAP].

A) mammary tumors - estrogen levels

Comment
NRDC argues that the failure to demonstrate an increase in serum estradiol levels after atrazine exposure refutes the hypothesis that a hyper-estrogenic state develops in SD rats, thereby leading to mammary tumors.

HED Response

The postulated mode of action is that atrazine exacerbates and accelerates reproductive aging in the SD female rat, causing an earlier onset and higher incidence of mammary gland tumors. The key events in this process include suppressing the pituitary LH surge, thereby prolonging estrous and attendant peak estrogen levels which leads to mammary gland tumors. This postulated mode of action is supported by the LH data and data that show that atrazine treated SD rats maintain constant estrous. Thus, it is not hypothesized that there is an increase in estrogen levels *per se* but that the estrogen-responsive tissues are exposed for an extended period of time to estrogen because of prolonged estrous. In chronic bioassays on natural and synthetic estrogens, it has been established that prolong stimulation of the mammary gland with estrogen leads to development of adenocarcinomas. NRDC cites 3 studies which they state demonstrate decreases in measured estradiol levels following atrazine exposure to SD female rats. However, in the Eldridge *et al.*, study (1993), which was not cited by NRDC, estradiol levels were elevated at 3 months in the atrazine-treated Sprague-Dawley female rats compared to the control rats at three months. Although the SAP noted that there is a lack of robust data on hormones in the atrazine database, the SAP stated that the database on atrazine strongly supports the hypothesis that prolonged exposure to estrogen produced by the ovary is requisite for development of the mammary tumors observed.

B) mammary tumors - lengthening of estrous

Comment

NRDC argues that EPA fails to explain the discordant finding within its proposed paradigm; *i.e.*, Fischer rat shows lengthening of estrus but no mammary tumors [Simic (1994) - J Appl Toxicol 14(6): 401-404]. Since lengthening of estrus is part of the mode of action, this finding demonstrates, according to NRDC, that the hypothesized MOA is not the only [or even the most important] MOA.

HED Response

In the paper cited by NRDC, the prolonged estrous cycle in the Fischer 344 rat was characterized by extended diestrous, in contrast to prolonged estrous in SD rats. In another paper not cited by NRDC [MRID 43598613], the effects of atrazine exposure [100 and 300 mg/kg/day for 2 weeks] on estrous were compared in SD and Fischer 344 rats. The SD female rats exhibited a treatment-related lengthening of the estrous cycle and an increased number of days characterized by cornified epithelial cells. This resulted in a greater percent of the cycle days spent in estrous and reduction in the percent of the cycle days spent in diestrus. Fischer rats also exhibited a significant trend toward cycle lengthening, but this was due to reduction in the percent of cycle spent in estrus and a concomitant increase in diestrual days. According to the authors, these findings suggest that treatment with atrazine at the dose levels used may result in prolonged exposure to endogenous estrogen in the SD but not the Fischer 344 rat.

In comparable studies in the Sprague-Dawley and Fischer 344 rats, atrazine exposure up to 400 ppm had no effect on the percent days in **estrus** in the Fischer rat or mammary gland tumor incidence [[Thakur, A. K. (1991). MRID 42146101] whereas the SD rats [Thakur, A. K. (1991), MRID 42085001] displayed an earlier appearance [after 9 months of treatment] of altered estrous cycles characterized by an increase in the percent days in estrus. Disrupted estrus cycles in SD female rats precede the appearance of mammary gland tumors in both control and treated groups, the effect of atrazine is to make both of these events occur earlier. The estrus and mammary gland tumor results reinforce the view that female SD rats display an earlier disruption of the estrus cycle than do control (untreated) animals and develop mammary gland tumors earlier. Unlike SD rats, control Fischer-344 female rats do not display abnormal estrous cycles until late in life and do not develop a high incidence of mammary gland tumors. The mode of action for SD female rats is further confirmed by data showing that Fischer -344 rats, which have a different reproductive senescence, do not form atrazine-related mammary gland tumors.

The SAP stated that tumorigenesis in female F-344 rats may have been obscured by the decrease in body weight and that a proper statistical test should be employed. EPA performed such analyses [using Gaylor and Kodell, 1999] of the mammary tumors in the F-344rats. The body-weight adjusted analysis of the data indicates that there is no statistically-significant, dose-response trend in tumor incidence.

C) mammary tumors - male mammary tumors in F-344 rats

Comment
NRDC argues that although the mammary tumors observed in male F344 rats appeared late in the study [Pinter (1990) - Neoplasms 37: 533-544], they add to the weight-of-evidence.

HED Response
As discussed previously by the SAP, a proper age-adjusted analysis of the tumor data results in the conclusion that the tumors appear to be due to increased survival and not to atrazine exposure.

D) mammary tumors - ovarian cycle disruption in pigs

Comment
NRDC believes these data [Gojermac (1996) - Toxicol Lett 85(1):9-15] indicate that atrazine disrupts ovarian cycling, inhibits estrus at low doses, and causes multiple ovarian cysts in the pig, and these data should not be ignored.

HED Response
These data were considered previously. It was determined that they are of limited value with respect to the mode of action assessment. These data suggest that atrazine may affect reproduction in pigs. However, there are several aspects of the study that hinder interpretation of the findings. Although the authors conclude that atrazine prolonged the estrus cycle, this endpoint [delayed estrus] was not adequately examined. There is no information regarding the frequency of the checks for estrus each day or whether the checks were preformed daily. The pigs may have had an undetected estrus before the expected estrus; i.e., short cycles. The paper states that the duration of estrus and the length of the estrus cycle were monitored for two cycles for each pig prior to study start, but no data were provided. It is not apparent whether any control pigs were also monitored prior to the start. In the Methods section of the paper, it states that after the last blood sampling [day 24] and checking the next expected estrus, the animals were sacrificed 7 days after the last blood sampling. It is unclear whether the pigs were monitored for the next expected estrus prior to day 24. According to The Merck Veterinary Manual, the

estrous cycle is **18**-24 days [average 21] in sows and gilts.

No hormone data were provided for the dosing period [days 1-19]. Blood samples [for hormone assessment] were collected three times in 6 hours on the first five days post dose [estrus cycle days 20-24]. It is noted that Figure B [control] of the paper shows estrus day 22 to be estrus day 0 also. It is not clear whether this is the day when the control displayed estrus or what was considered to be the next expected estrus.

The estradiol values in the treated pigs did not fluctuate much over the 5-day monitoring period, and they do not appear to be elevated compared to the control values. The progesterone levels were low [atrazine pigs] in the first sample, which might be expected if treatment had induced early luteolysis or the pigs were experiencing short normal cycles. The progesterone levels thereafter increased daily, indicative of new luteal function, not persistence of corpora lutea. Although the profiles of these hormones appear to be different between the treated and control pigs [Figures A and B], there may only be a shift in time. Also, this may be a similar situation as observed in the Fischer 344 rat [prolonged cycle not associated with increased estrogen exposure]. Interpretation of the findings in the pig is further hindered since there are no LH data to determine whether the pigs failed to have an ovulatory surge of LH.

Other limitations with this study include the small sample size [4 animals] and the lack of dose-response data [only one dose evaluated].

E) mammary tumors - non-estrogenic mechanism/increased susceptibility/tumor promotion

<u>Comment</u>
NRDC believes there is new evidence [references Fenton, 2002] that demands a complete reevaluation of cancer risk. The Fenton study found that Long-Evans [LE] rats prenatally-exposed to atrazine and subsequently challenged [PND 45] with known mammary carcinogen [DMBA] were more likely to develop mammary gland tumors/more tumors/larger tumors than LE rats exposed to atrazine or DMBA alone. The paper also reported that atrazine exposure alters pubertal mammary gland development *via* a non-estrogenic mechanism, thereby supporting a mechanism by which pubertal alterations may predispose individuals to tumor development.

<u>HED Response</u>
It should be noted that the Fenton *et al.*, data are preliminary and have not been fully peer reviewed. The preliminary work reported in an abstract by Fenton and Davis (2002), an investigator in NHEERL's Reproductive Toxicology Division, suggests that gestational exposure to atrazine may affect the developing mammary gland. This preliminary work indicates that

atrazine causes a developmental delay in mammary gland maturation, which lengthens the window of susceptibility to the carcinogen DMBA. In another abstract, Greiner, Youngblood, and Fenton (2002) suggest that atrazine decreases puberty-induced mammary gland development by altering normal pituitary functions. The Fenton *et al.*, data do not provide evidence of a direct cancer mode of action that may be operative in humans given these studies involve co-treatment with a well known mutagenic carcinogen. This work is, however, consistent with the other reported findings from Dr. Ralph Cooper's laboratory (e.g.,Laws et al., 2001, Stoker et al., 2001) that atrazine affects/causes developmental effects or delays (e.g., delayed puberty) by altering hypothalamic-pituitary function. EPA agrees that atrazine's ability to affect pituitary function and result in developmental effects should be assumed to be relevant to humans. The NOAELs and safety factors used in the atrazine assessment addresses this preliminary study.

F) Wilms tumor - data on tadpoles

Comment

Reference [Tavera Mendoza Abstract presented at SETAC 22nd Annual Meeting, 11/13/01] is made to a recent study that found that tadpoles exposed to atrazine during gonadal differentiation developed renal embryonic adenosarcoma [Wilms' tumors]. It is stated that disruption of the WT-1 gene can occur in both the frog and human, and that this alteration has been linked to Wilm's tumor in both species [referencing the above]. NRDC believes that this report merits careful consideration.

Additionally, NRDC associates studies reporting association of pesticide exposure of the parents [Sharpe, *et al.*, Epidemiology study in Brazil] and an increase in this tumor in children. NRDC wants this tumor finding as part of the weight of evidence in the cancer assessment.

HED Response

The potential of atrazine to alter the WT-1 gene is not based on data and is speculation at this time. There are similarities and differences in development and regulation by hormones among vertebrates, and the effects of atrazine on amphibians and how they may relate to humans is under review. EPA is planning to convene an independent scientific peer review [the FIFRA Science Advisory Panel (SAP)] of information related to potential effects of atrazine on amphibians sometime in mid-2003.

With respect to the other cited studies, the associations described in humans [Sharpe, *et al.*] were with pesticides in general (insecticides and herbicides] used in farm work. Information on specific pesticides used [atrazine] was not obtained. Although the results reported in some studies suggest parental exposure to pesticides may be related to the subsequent development of cancer in the offspring, other explanations cannot be excluded. Additionally, there are numerous other studies not cited by NRDC that indicate it unlikely that environmental exposures play a major role in the etiology of Wilms tumor.

In a case-control study conducted with histologically confirmed neuroblastoma cases among New York State residents [Kerr, M. A., *et al.* Cancer Causes Control (2000), Aug. 11 (7): 635-643], the odds ratios were significantly elevated for maternal and paternal occupational exposure to various substances, including *insecticides*; herbicides [atrazine] were not mentioned. However, the authors concluded that due to the uncertainty of the biologic plausibility of these associations and the possibility of alternative explanations, the results should be interpreted cautiously.

In a related issue, but one not involving cancer *per se*, there is a growing concern that exposures to a wide-range of endocrine disrupting chemicals (EDCs) are associated with feminization of birds, fish, alligators, and other animals in the environment. The concern has been raised that EDC related feminization of males observed in the ecosystem is also occurring in humans. This is an emerging area of concern, and the scientific community and other interested parties are engaging in discussions. As mentioned above, EPA is planning to convene an independent scientific peer review [the FIFRA Science Advisory Panel (SAP)] of information related to potential effects of atrazine on amphibians sometime in mid-2003.

G) lymphoma - several studies

Comment
NRDC states that Non-Hodgkin's lymphoma has been on the rise in recent decades, and several studies are cited and discussed.

HED Response
As stated by the SAP previously, "To summarize, there are a few epidemiologic studies that suggest a possible association between atrazine (or triazine) exposure and NHL and ovarian cancer. However, lack of multiple studies showing an association and internal inconsistencies in the studies available indicates that the human studies by themselves do not make a strong case for an association." Please refer to the Interim Reregistration Eligibility Decision (IRED) for further discussion.

H) human cancer - prostate cancer, ovarian cancer, testicular cancer, breast cancer, leukemias/lymphomas

Comment
NRDC discusses Syngenta's St. Gabriel facility data and other epidemiology data and states that these data should not be ignored. NRDC believes the epidemiology results are "not likely to be due to chance", and are "almost certainly related to herbicide exposure". Please refer to the memoradum entitled, "Review of Additional Data on Potential Atrazine Exposure and Review Comments Submitted by Syngenta and NRDC on Atrazine Cancer Epidemiology Study: "Follow-up Study of Cancer Incidence Among Workers in Triazine-related Operations at the Vnovartis St. Gabriel Plant" by E. Delzell et al. D287278, J. Blondell, January 15, 2003 and the Interim Reregistration Eligibility Decision (IRED) for further discussion.

HED Response
As stated above, the SAP considered the available epidemiology data and concluded that there are

a few epidemiologic studies that suggest a possible association between atrazine (or triazine) exposure and NHL and ovarian cancer. However, lack of multiple studies showing an association and internal inconsistencies in the studies available indicates that the human studies by themselves do not make a strong case for an association.

HED's review of the data on increased incidences of prostate cancer at the St. Gabriel plant in Louisiana is as follows (see memorandum, J. Blondell, 1/15/03, Review of Additional on Potential Atrazine Exposure and Review Comments Submitted by Syngenta and NRDC on Atrazine Cancer Epidemiology Study: "Follow-up Study of Cancer Incidence Among Workers in Triazine-related Operations at the Novartis St. Gabriel Plant by E. Delzell et al." DP 287278):

> "*It appears that most of the increase in prostate cancer incidence at the St. Gabriel plant in Louisiana is likely due to intensive PSA screening. The study was insufficiently large and suffered from other limitations which prevent ruling out atrazine as a potential contributor to the increase observed. On balance, however, a role for atrazine seems unlikely because prostate cancer was found primarily in active employees who received intensive PSA screening, there was no increase in advanced tumors or mortality, and proximity to atrazine manufacturing did not appear to be correlated with risk. Atrazine has been tied to inflammation of the prostate in laboratory animals and changes in testosterone levels at high doses. However, neither condition has been tied to the increased risk of prostate cancer and HED concludes the animal data do not provide biologically plausible evidence to support atrazine as a cause of prostate cancer.*
>
> *Other cancers besides prostate were found to have an elevated, though not statistically significant, increase in risk at the St. Gabriel plant. Other studies have suggested an increased risk for ovarian, breast, and other cancers, including non-Hodgkin's lymphoma. However, these studies are at best preliminary and should not serve as a basis for implicating atrazine as a human carcinogen due to their methodological limitations.*"

I) other modes of action [page 24]

<u>Comment</u>
NRDC wants EPA to fully explore other modes of action and relevance to humans. They believe that EPA has failed to adequately consider other modes of action. Although NRDC states that it is clear that atrazine acts as an endocrine disruptor and that one of the modes of action involves the hypothalamic-pituitary-gonadal axis, they are not convinced that this is the only mode of

action. NRDC believes there is evidence of at least three other modes of action.

> (1) aromatase activity -Aromatase is a cytochrome p450 enzyme that converts steroids or androgens to estrogens, thus increasing estrogen levels in the body. It is found in different species (both mammalian and nonmammalian) and in various tissues (mammary gland, ovary, bone, brain, etc). Data available are primarily from studies in frogs, fish and alligators, in addition to data on human adrenocortical cells [*in vitro*]. NRDC says EPA has not explained why it is ignoring this critical information on an alternative mode of action.

<u>HED Response</u>
No new data are provided by NRDC on any of the other modes of action. The SAP was asked to comment on whether alternative modes of action (re: mammary tumors) have been sufficiently discussed and ruled out by the Agency. The SAP stated "There are no data that would suggest other plausible modes of action. The increased level of hormones and the increased level of hormones alone, can account for the increased incidence of mammary tumors in Sprague Dawley female rats. The proposed mode of action is plausible and each step in the pathway has been shown to be affected in atrazine treated rats.

Previously, OPP concluded that it is plausible that **enhanced** aromatase activity may have some influence on the development of mammary tumors in SD female rats. However, whether or not enhanced aromatase activity is a significant contribution to the carcinogenicity, or other effects, of atrazine remains to be determined. EPA acknowledged the fact that an increase in aromatase activity would be consistent with dose-response increases in estradiol and estrone and decreases in testicular testosterone noted in a study that examined the effects of atrazine on pubertal development. The doses that resulted in effects on these hormones were well above doses that led to reproductive/developmental effects. Additionally, it was acknowledged that it is plausible that enhanced aromatase activity may have some influence on the development of mammary tumors in SD female rats; however, there are no data to date on whether enhanced aromatase activity significantly contributes to the carcinogenicity observed. The effect of the chlorotriazines on aromatase remains an active research issue, in general.

The EPA's National Health and Environmental Research Laboratory (Dr. Ralph Cooper's laboratory) have recently evaluated the effects of atrazine and DACT on aromatase activity in the rat. Preliminary results show that DACT does not effect aromatase activity and atrazine actually causes a **decrease** in aromatase, but only at high doses. Based on the weight of evidence, enhancing aromatase activity does not appear to be a mode of carcinogenic action, particularly given the recent findings of Ralph Cooper. Further, if this were a primary mode of action, a more consistent finding of tumors at estrogen sensitive sites would be anticipated in the rodent carcinogenicity studies. Lastly, the June 2000 FIFRA Scientific Advisory Panel was specifically asked about OPP's assessment of other possible other modes of carcinogenic action, and the SAP agreed that there is an insufficient basis to link effects on aromatase to the mammary gland tumor response in female Sprague Dawley rats.

With regard to research data relating to the effects of atrazine on amphibians, EPA has not yet reached conclusions on these data, and therefore does not have any specific comment on these research efforts. EPA is planning to convene an independent scientific peer review [the FIFRA Science Advisory Panel (SAP)] of information related to potential effects of atrazine on amphibians sometime in mid- 2003.

> 2) 16-alpha-hydroxyestrone - NRDC states that there is some evidence that atrazine may affect estrogen metabolism, resulting in a greater production of a mutagenic metabolite.

<u>HED Response</u>
In 1993, it was postulated by Davis et al. that the 16α-hydroxyestrone is a type of estrogen which results in the formation of breast cancer in women. But, this hypothesis is in contrast to the work of Aldercreutz et al., 1994 which showed through epidemiologic studies that involvement of estrogen metabolites as a risk factor for breast cancer, is at best circumstantial. Furthermore, more recent work by Ursin et al., 1999 indicates that 16α-/2-hydroxyestrone ratios are not predictive of breast cancer risk in patients. In 1994, Bradlow et al., reported using MCF-7 cells that atrazine might increase the production of 16α-hydroxyestrone by altering the intracellular metabolism of estrogens. However, more recent studies by Safe and coworkers indicate that decreases or increases in 16α-/2-hydroxyestrone ratios do not predict mammary gland cancer potential. McDougal et al., 1997 evaluated the effects of atrazine and the effects of a variety of chemicals known to inhibit or induce mammary gland tumors in rats on the estradiol-2-hydroxylase activity in the MCF-7 model (McDougal et al, 1997). Atrazine reduced estradiol-2-hydroxylase activity, and no correlation between cancer (or anticancer) potential and estradiol-2-hydroxylase activity could be demonstrated. McDougal and Safe, 1998 studied the effects of several pesticides, mammary gland carcinogens and anti-estrogens on estradiol, 16α- and 2-hydroxylase activities and 16α-/2-hydroxylase ratios in MCF-7 cells. These results also indicated that in MCF-7 cells treated with different chemicals both increases and decreases in 16α-/2-metabolite ratios were found and thus 16α-/2-metabolite ratios were not predictive mammary gland carcinogens.

This issue was addressed previously [in Part B of the May 2000 EPA atrazine document], and NRDC has not provided any new data.

3) metabolite N-nitrosoatrazine - NRDC points out that this metabolite is mutagenic, and a mutagenic MOA on the part of a metabolite would imply a cancer risk in humans without a threshold. NRDC states that the overall scientific evidence indicates that atrazine may be acting both as an initiator and as a promoter of cancers in hormonally-sensitive organs.

<u>HED Response</u>
Again, it is pointed out that the SAP addressed this issue in 2000. The role nitrosoatrazine may play in cancer development in humans, is questionable. Although the mutagenic compound *N*-Nitrosoatrazine (NNAT) can be formed *in vitro* when atrazine and nitrite are mixed at an acid pH, and because nitrites and atrazine can be found together in drinking water, concern has been raised about this mutagenic chemical. Although the hypothesis has been advanced that NNAT can be formed in the acid pH found in the stomach, the formation of NNAT in the stomach *in vivo* has yet to be demonstrated. If indeed the mutagenic compound NNAT could act as an initiator of the cancer process, one would expect NNAT to be carcinogenic. However, the cancer bioassays in female Swiss mice and female Wistar rats failed to show a carcinogenic response following NNAT exposure. Since the June 2000 SAP, there have been no new data on NNAT and NRDC has not provided any new data to the Agency.

FQPA Safety Factor Issues

A. **2-hydroxyatrazine** - NRDC considers the lack of a FQPA safety factor for 2-hydroxyatrazine to be a mistake since it shows similar toxicity [adverse reproductive endpoints] as atrazine and DACT. NRDC wants a 10X FQPA safety factor on this metabolite also.

<u>HED Response</u>
Unlike Atrazine, 2-hydroxyatrazine, did not cause a delay in vaginal opening but did cause a minimal delay in preputial separation (Laws *et al.*, 2002). Furthermore, there was no increase above control levels in the incidence of mammary gland tumors or tumors of any type in a two-year chronic/carcinogenicity study on 2-hydroxyatrazine (Chow and Hart, 1995). In a recent registrant sponsored study [Eldridge, J. C., Minnema, D., Breckenridge, C. B. , et al.; SOT, March 2001], 2-hydoxyatrazine did not suppress the LH surge. However, Dr. Ralph Cooper at the EPA's NHEERL is currently evaluating whether this metabolite alters the LH surge. However, based on available data, it can not be concluded that 2-hydroxyatrazine shares the same neuroendocrine mode of action with atrazine. Thus, the data do not raise the same issues regarding the potential susceptibility of the young due to its neuroendocrine mode of action. Furthermore, no increase in sensitivity was observed following exposure of rats during gestation

days 6-15. Data available on 2-OH atrazine include a subchronic oral toxicity study and a chronic oral toxicity study in rats, a rat developmental toxicity study, and mutagenicity studies. Reproductive organ toxicity was not observed in any of these studies. In a recent study [NHEERL], pregnancy loss was observed at 300 and 500 mg/kg/day, but not at 100 mg/kg/day, following 2-OH atrazine exposure of LE dams on gestation days 6-10.

In addition, although hydroxyatrazine is a metabolite of atrazine, it is structurally dissimilar to atrazine in that it lacks chlorine. Plants are capable of metabolizing atrazine to hydroxyatrazine. In plants it is the major metabolite. Bacteria are also able to metabolize atrazine to hydroxyatrazine. However, animals do not metabolize atrazine to hydroxyatrazine. Ruminants may receive hydroxyatrazine in their diets through forages and fodders, but these residues are not anticipated in the meat and milk that humans eat. Dietary exposure to hydroxyatrazine is expected to be minimal (< 1% of the cPAD). Exposure to hydroxyatrazine in drinking water is also expected to be insignificant. The EFED has determined that although occasional contamination of surface waters by hydroxyatrazine cannot be ruled out, in general, hydroxyatrazine is unlikely to contaminate surface water to the same degree as atrazine and some of the chlorinated metabolites. This qualitative assessment is based on monitoring data, albeit limited, and plant metabolism as the main pathway of hydroxyatrazine formation.

> As stated in the April 16, 2002 risk assessment, ..."*The available toxicity database for hydroxy atrazine was examined. Toxicity studies submitted under Subdivision F Guideline requirements (i.e., subchronic, chronic/carcinogenicity, and developmental) indicate that the kidney is the primary target organ for hydroxyatrazine associated toxicity. Hydroxyatrazine appears to crystallize in the serum leading to the formation in the blood stream of hydroxyatrazine crystals. These crystals cause direct physical damage to the kidney. This crystallization phenomenon has not been observed with atrazine or any of the chlorinated metabolites of atrazine. Hydroxyatrazine is not a chlorinated metabolite of atrazine, and is not considered to share a common mechanism of toxicity with atrazine.*
>
> *There is no evidence for increased susceptibility of rat fetuses following in utero exposure to exposure to hydroxyatrazine in the prenatal developmental toxicity study in rats. However, neither a prenatal developmental study in the rabbits nor a two-generation reproductions study conducted with hydroxyatrazine in rats is available. In the prenatal developmental toxicity study in rats there was a statistically significant decrease in fetal weights and an increase in incompletely ossified interparietals and hyoid bones was seen in the presence of maternal toxicity. The HIARC determined that these findings lacked toxicologic significance. While special studies and an open literature study indicate a neuroendocrine toxicity in the CNS of rats following atrazine exposure, overt signs of*

neurotoxicity were not seen in the toxicology studies for hydroxyatrazine. ***The neuroendocrine alterations mentioned above would not be expected to be seen following hydroxyatrazine exposure.*** *Based on the above findings, the FQPA Committee made the following determination:*

The FQPA Safety Factor Committee (SFC) following review of the hazard and exposure (food, water and residential) data recommended that the FQPA safety factor be removed (1x) when assessing the hydroxy-metabolites since:

1. *There was no evidence of increased susceptibility in the prenatal developmental toxicity study in rats with hydroxyatrazine;*

2. *There is no evidence of neurotoxicity from the submitted toxicity studies;*

3. *The neuroendocrine effects described for atrazine are postulated to be part of a cancer mode of action for atrazine. Because hydroxyatrazine is non-carcinogenic, the current belief is that the neuroendocrine effects described for atrazine are not occurring following hydroxyatrazine exposure;*

4. *The dietary and non-dietary exposure assessments do not underestimate the potential exposures for infants and children; and*

5. *The drinking water exposure concerns expressed for atrazine and the chlorinated metabolites do not apply to hydroxyatrazine, given its dissimilar toxicological profile and environmental fate properties that indicate that hydroxyatrazine is less mobile in soil/water systems."*

The FQPA decision was not based solely on toxicity, but also on exposure concerns. In the case of hydroxyatrazine, exposure concerns <u>are minimal</u>. Although hydroxyatrazine has shown altered pregnancy maintenance (a LOAEL of 50 mg/kg/day for atrazine and 91 mg/kg/day for hydroxyatrazine) and delayed parturition (a LOAEL of 50 mg/kg/day for atrazine and 91 mg/kg/day for hydroxyatrazine) like atrazine, these effects occurred at higher doses than for atrazine.

B. **magnitude of safety factor** - NRDC wants a larger safety factor applied, since they consider the FQPA safety factor of 10X, which accounts for both exposure and risk uncertainty, as unlikely to sufficiently capture the magnitude of uncertainty within this assessment.

HED Response

Retention of the FQPA safety factor of 10X was based on residual concerns for both developmental effects and exposure. For all the reasons listed in NRDC's comment, i.e., lack of monitoring data on degradates, concern over peak exposures not captured, and extent of exposure not captured in the available databases, and residual concerns regarding toxicity, the FQPA Committee decided to retain the full 10X FQPA safety factor. The Committee met twice to consider the FQPA safety factor and both times returned a decision to retain the 10 X for dietary assessments because of these residual toxicity and exposure concerns. This decision was made in light of the fact that atrazine has the most extensive drinking water/raw water monitoring database of any pesticide, and one of the most if not the most extensive toxicity database for a pesticide.

The HIARC concluded that due to residual concerns [concern of the potential neuroendocrine effects of atrazine exposure throughout all critical developmental periods, which have not been adequately characterized], the **hazard-based** special FQPA safety factor was required. However, the HIARC concluded that it could be reduced to 3X. This was based on a comparison of the lowest NOAEL available in the young animal [6.25 mg/kg/day; 31-day pubertal development study] with the lowest NOAEL in the adult animal [1.8 mg/kg/day ; 6-month LH surge study]. This comparison suggests that the young would not be expected to be an order of magnitude more sensitive than adults. A similar comparison using studies of comparable duration also indicates that the young would not be expected to be an order of magnitude more sensitive than the adult animal. For example, the NOAEL determined for delayed sexual maturation [20 days exposure] in the female rat is 25 mg/kg/day compared to the NOAEL of 5 mg/kg/day in the 28-day exposure study in adult females [LH surge attenuation and estrous cycle alterations].
In addition, the NOAELs determined for delays in preputial separation and delayed sexual maturation are 6.25 mg/kg/day [males]/25 mg/kg/day [females], respectively. These endpoints, which are indicators of pubertal hypothalamic-pituitary-gonadal related effects, show NOAELs that are 3.5X and 14X, respectively, greater than the adult NOAEL for LH effects [1.8 mg/kg/day].

Regarding exposure based uncertainty, the exposure assessments do not underestimate exposure. Data collected from a targeted set of CWS with contamination histories or MCL violations were monitored frequently to determine maximum exposures in these most highly exposed CWS. CWS with compliance monitoring data also represent a targeted data set because these CWS are the ones in known atrazine use areas. Altogether, as explained in the risk assessment documents, the data set used was biased to reflect the high-end exposures occurring in the US. In addition, the exposure assessments utilized maximum concentrations for one-day, 90-day, and annual average exposures to estimate exposure and compared these exposures to the most sensitive endpoint (lowest) in the toxicity database to which a 1000-fold uncertainty factor has been applied.

Having said that, it is likely that the data sets used may not have identified all CWS with exposures of concern, because of the limitations on the monitoring data previously discussed in the risk assessment and at the technical briefing. However, it is different to say that the extent of exposure, i.e., the exact number of individuals exposed at levels of concern, is not known versus saying the high-end exposure as a dose (in mg/kg/day) has been underestimated. It is fair to say that the CWS identified as of concern represent the high-end exposures (doses in mg/kg/day) for the US population, but also possible that not all CWS with high-end exposures have been identified.

C. **underestimate of risk** - NRDC considers the lowest dose tested in the 6-month LH surge study to be an **effect** dose [see discussion of this aspect elsewhere]. Although NRDC supports the EPA conclusions that the neuroendocrine effects associated with atrazine exposure are of extreme concern, are relevant to all populations, and are of greatest concern to fetuses, infants, and children, NRDC states that the demonstrated ability of atrazine and its metabolites to disrupt normal neuroendocrine function will impact growth, development, reproduction, immune, and metabolic functions. NRDC continues by pointing out that "human exposures to abnormal levels of LH during early life may permanently imprint on the hypothalamic-pituitary-gonadal pathway, thereby determining the ability to respond normally to testosterone and other gonadal hormones later in life. The response of the central nervous system to the gonadal hormones during childhood and puberty is tightly regulated by neurotransmitters in the brain, mainly glutamate and GABA (gamma-aminobutyric acid). Without the normal hormonal levels during development of the fetal and infant nervous system, the ability to elicit normal responses to gonadal hormones later in life may be compromised. It is likely that exposure of the infant and toddler to levels of atrazine during early life, at levels which interfere with LH activity, may have adverse effects on pubertal development, and on later reproductive function, negatively impacting on the life-long health of an exposed person."

HED Response
NRDC's comments are essentially what was stated in the risk assessment. Atrazine is one of the best studied pesticides, and there is an extensive toxicology database on its mechanism of toxicity. The perturbation of the hypothalamic-pituitary-gonadal axis is the primary and only established mode of action of atrazine. Based on the nature of the effect of concern [neuroendocrine disruption] and uncertainties with respect to possible effects from exposure throughout development, which have not been thoroughly examined, a potential for noncancer effects due to atrazine's ability to disrupt hypothalamic-pituitary function could not be discounted. The endpoint selected for the risk assessments [LH surge attenuation and estrous cycle alterations] serves as a **surrogate** for the effect of atrazine on the hypothalamic-pituitary axis/function, and the NOAEL selected is the lowest NOAEL in the database for the endpoint of concern and is considered protective for all population subgroups.

However, as previously stated, EPA's position is that 1.8 mg/kg/d is a NOAEL in the 6 month LH surge study by Syngenta. EPA believes it is justified in using 3.6 mg/kg/d as a LOAEL for this endpoint. The rationale for the selection of 3.6 mg/kg/d as a LOAEL and 1.8 mg/kg/d as a NOAEL for suppression of the LH surge is based on a weight of evidence argument. There is a dose response trend for suppression of the LH surge. While the 3.6 mg/kg/d dose does not represent a statistically significant decrease in the amount of LH, this dose response trend is supported by the statistically significant difference in vaginal cycling at 3.6 mg/kg/d. Vaginal cycling data tend to be less variable than LH data. Thus, EPA acknowledges that selection of 1.8 mg/kg/d as a NOAEL for LH suppression is conservative, but errs on the side of health protection. Although there is one statistically significant response for suppression of the LH surge in the 1.8 mg/kg/d dose group for one time point, this is not sufficient evidence to designate 1.8 mg/kg as a LOAEL, particularly in light of the fact there were no statistically significant differences found for vaginal cycling at this dose.

Farm Worker Children and Worker Risk -

Comment
NRDC believes OPP has not addressed risks to farm worker and their children's adequately in the risk assessment under FQPA.

HED Response

HED defers to the IRED for further discussion and response to this comment.

High-End Exposures -

Comment
EPA cannot willfully ignore high-end exposures. EPA does not quantify the risks to all individuals. The assessment does not address the top 0.1 percent of intermediate-term drinking water exposures.

HED Response
HED disagrees with the NRDC that high-end exposures were ignored in the risk assessment. The CWS targeted for probabilistic assessment represent those CWS in the data set with the highest exposures, and are therefore a biased set of CWS, biased towards the high-end of known exposures. Therefore, these CWS represent the high-end of seasonal drinking water exposures anticipated by HED. Average 90-day exposures to atrazine in drinking water at the 99.9th percentile of exposure were compared to the selected endpoint for intermediate-term effects (0.0018 mg/kg/day). Because these CWS represent the highest exposures anticipated throughout the US, the 99.9th percentile exposure at each one of these CWS is likely to represent greater than the 99.9th percentile exposure on a national level. Without data on atrazine for all CWS, it is difficult to say where the percentile of exposure for CWS with high-end exposures would fall on a national level other than to say, it would fall somewhere between the 99.9th and 100^{th} percentiles. However, it can be said that the CWS identified with risk estimates of concern represent high-end exposures and serve ~ 230,000 to 240,000 people. For these CWS risk estimates of potential concern have existed at each of these CWS at some point between 1993 and 2001 for infants < 1 year old.

In general, when acute food exposures are estimated, they are estimated for the entire US, and the 99.9th percentile of exposure represents the 99.9th percentile exposure for the entire US population. Food exposures of zero are included in the probabilistic assessments. Unlike food exposure, HED considered drinking water exposures to atrazine on a system-by-system basis, rather than conducting one assessment inclusive of exposures at all community water systems (CWS). The drinking water exposure assessment was based on those CWS for which data on atrazine were available, located in the high use areas for atrazine. The assessment did not include CWS with zero exposure because of a lack of use of atrazine in the vicinity. Consequently, by definition, the drinking water exposure assessments are biased towards the high-end of exposures in CWS targeted by a history of atrazine use or contamination.

Percent Crop-Treated and Anticipated Residues -

Comment
The EPA may only use percent of crop-treated data for dietary chronic risk assessments, and before using the data must show the data are reliable and do not underestimate exposure. Since

anticipated residues (ARs) were used in the dietary assessment, this data must be provided within 5 years of establishing a tolerance on ARs to verify that the tolerance established based on the ARs do not underestimate actual residue levels.

HED Response

The issue of using percent-crop-treated data in acute dietary risk assessments has been addressed by OPP before in a variety of responses to public comments, SAP reports, and policy documents. This comment was addressed in a previous response to comment document but is reiterated here. OPP believes that the use of probabilistic techniques to perform acute dietary exposure analyses allows a more realistic evaluation of exposures through food and permit the risk manager to make decisions which reflect a truer picture of risk. Older methods used by OPP for acute dietary risk assessments were limited to the assumption that 100% of the crop was treated, and the resulting acute risk estimates were considered "high end" or "bounding"; these provided little information to the risk manager on the variability or uncertainty associated with the risk estimate nor any indication of how probable such high-end exposures were or what might be more expected levels of exposure. In short, then, OPP believes that its use of probabilistic techniques in acute risk assessments are entirely appropriate and that the use of percent crop treated is an important consideration that is a critical and necessary component of any probabilistic risk assessment.

The commentary has stated that "acute risk assessments should never include any averaging of exposures over time, which is what using percent crop treated data does." EPA's position is that using percent crop treated does NOT average exposures over time, but rather instead accounts for the *probability* (frequency) of an exposure occurring. More specifically, this percent crop treated factor determines the proportion of crop that is assumed to have zero residues (calculated as 1-PCT). Probabilistic assessments as performed by OPP do not "adjust" the measured residues or average exposures over time, but rather assign a probability of encountering a residue in any individuals daily food consumption. The difference between using percent crop treated as an adjustment factor (an invalid approach) and using it as an assigned probability (a valid approach) is illustrated below:

<table>
<tr><td colspan="4">Illustration of Valid and Invalid Means of Incorporating Percent Crop Treated (%CT) Into an Acute Probabilistic Assessment</td></tr>
<tr><td colspan="3">Invalid</td><td>Valid</td></tr>
<tr><td><u>Available Residue Values</u>

0.34 ppm
0.26 ppm
0.49 ppm
0.86 ppm
0.43 ppm</td><td><u>%CT</u>

10</td><td><u>Resulting Residues</u>

0.034 ppm
0.026 ppm
0.049 ppm
0.086 ppm
0.043 ppm</td><td>90% Probability of residue being " zero"

and

10% Probability of residue being either 0.34 ppm, 0.26 ppm, 0.49 ppm, 0.86 ppm, or 0.43 ppm</td></tr>
</table>

In an acute probabilistic exposure assessment, using the valid approach outlined above, a distribution of residue values would be constructed consisting of 45 zeros and the 5 residue values shown. This provides a 90% chance (probability) that a residue concentration of zero will occur and a 10% chance that a residue value of either 0.34 ppm, 0.26 ppm, 0.49 ppm, 0.86 ppm, or 0.43 ppm will occur in the assessment. Each of the 5 residue values shown have an equal probability relative to each other (2%) of occurring in the assessment. OPP's probabilistic assessments ensure through successive iterations that all residue values in the constructed distribution occur in the assessment. Therefore, all of the residue values available will be represented (included) in the probabilistic assessment with the appropriate frequency with which they are expected to occur in the food supply. The use of the %CT factor in the acute probabilistic assessment ensures that the available residue data are neither over-represented nor under-represented in the assessment.

Percent-crop treated (PCT) data are updated regularly by the Benefits and Economic Analysis Division (BEAD). The original EPA estimate was based on the years 1990-1996. The

Quantitative Usage Analysis (QUA) dated January 10, 2001 included PCT estimates for the period for 1990 to 1997. Although EPA's most recent estimates are from 2000, any updated PCT analysis would include data from a broader range of years than 2000. Since the data from a period of 1990 to 2000, the most recent decade available, were used in the assessment, they are considered current, and up to date. BEAD regularly collects these data from a variety of sources, USDA NASS, the registrant, and marketing sources (DOANE's). HED believes the PCT data used to generate ARs in the atrazine risk assessment are current, and BEAD regularly collects these data on an ongoing basis negating the need to require any data from the registrant.

Anticipated residues (ARs) are used in the atrazine dietary risk assessments and were based on available PDP monitoring data, field trial residue data, plant metabolism study data, and tolerances. The available monitoring and field trial data are current and reflect the most recent use patterns and rates of atrazine. Monitoring data generally show that atrazine residues are not detected. The ARs based on metabolism data are very conservative in that they are based on levels of atrazine not normally detected in field trial studies or monitoring data because the residues are radio-labeled, and the analytical methods used to detect them are very sensitive. These data coupled with up to date PCT data result in dietary assessments that are highly refined and protective. For details, HED refers the reader to the document entitled, "Atrazine. Anticipated Residues and Acute and Chronic Dietary Exposure Assessments for Atrazine, Revised January 2001, January 18, 2001", available on the atrazine website.

Atrazine tolerances are not based on ARs . Tolerances for atrazine are based on field trial data submitted by the registrant under OPPTS guidelines. Field trial data reflecting the maximum labeled use rate, and minimum time to harvest, show for most foods consumed by humans, that residues of atrazine are non-detectable. For example, the corn grain tolerance was established at 0.20 ppm based on non-detectable levels of atrazine and its 3 chlorinated metabolites at the limit of quantitation (for the analytical method used) 0.05 ppm for atrazine and each metabolite (4 x 0.05 = 0.20). Monitoring data collected regularly under the PDP program support the field trial data and provide the necessary verification check on actual residue levels incurred in foods to ensure that tolerances are not underestimated. ARs are based on this monitoring data as well as field trial and metabolism data. ARs are used for the purposes of assessing dietary exposure, not for establishing tolerances.

Human Testing -

<u>Comment</u>

EPA used a flawed human study for dermal absorption. The dermal absorption study EPA considered is "poorly designed and non-probative from a scientific standpoint". The study in question used too few subjects (10) to account for variability in the population. Consideration of the dermal absorption study is inconsistent with EPA's policy "not to use human studies while their propriety is under review." The comment further urges EPA not to use results from human tests, and expresses concerns about the ethics of human testing under the Nuremberg Code.

HED Response

Because toxicity testing overall involves too few subjects (animal) to account for interspecies variability, OPP routinely applies a 10 uncertainty factor to all risk assessments to account for this uncertainty. The atrazine risk assessment includes the 10X uncertainty factor for interspecies variability. Therefore, it is EPA's position that the number of subjects in the dermal study does not preclude its usefulness in the risk assessment.

OPP is interested in reducing uncertainty where possible in its risk assessments. The statement that use of this study is inconsistent with EPA policy is over-broad and mischaracterizes EPA policy. EPA's December 14, 2001 policy announced that until we have a policy in place, we will not use third party human studies involving intentional exposure to toxicants for the purpose of defining or quantifying their toxic effects. Although the dermal absorption study is a third-party study and it did involve intentional exposure, its purpose was not to define or quantify toxic effects. Therefore we are not prohibited by the Agency's policy from considering or relying on this study.

Dermal Absorption while Showering -

Comment

Atrazine may be inhaled in water in the shower, and absorbed through the skin and mucous membranes.

HED Response

Previously, NRDC noted that exposure to atrazine in the shower was excluded from the risk assessment and that ignoring such exposures may underestimate risk. They gave examples of volatile organic compounds like benzene and chloroform for which inhalation of vapors account for 50% of exposure. HED provided the following response, "Atrazine is not a volatile chemical. Inhalation exposures are not anticipated as a major exposure pathway. Atrazine has a vapor pressure of 2.89×10^{-7} mm Hg at 25 C. The vapor pressure of benzene is 94.8 mm Hg at 25 C, and for chloroform is 197 mm Hg at 25 C. The comparison of vapor pressures of atrazine to compounds like benzene and chloroform shows that benzene is 333,333,333 times more volatile than atrazine, and chloroform is 666,666,667 times more volatile than atrazine. Clearly, inhalation through volatilization is the most significant exposure pathway for benzene and chloroform. To exclude exposure via inhalation in the shower for compounds like benzene and chloroform present in tap water would clearly be an error. It is not surprising that exposure via showering for these compounds accounts for 50% of total exposure to these compounds because of their high volatility. Equally clearly, however, given the low volatility of atrazine that is nine orders of magnitude less than organic solvents like benzene and chloroform, it can be seen that inhalation through volatilization is not a significant exposure pathway for a non-volatile, water soluble compound like atrazine."

Regarding absorption of dissolved atrazine through the skin and mucous membranes, given that exposure to atrazine in drinking water and food assumes a gut absorption rate of 100%, the oral exposure route is considered to be the dominant exposure pathway. Given atrazine's dermal absorption rate of 6%, atrazine dissolved in water and absorbed through the skin and mucous membranes is not expected to be a dominant exposure pathway.   HED did consider dermal absorption and inhalation of atrazine in its aggregate exposure assessments.   The aggregate risk assessments combine oral (dietary: food + drinking water) and non-dietary (toddler hand-to-mouth) exposures, with dermal and inhalation exposures as appropriate. These assessments consider dermal and inhalation exposure to the actual liquid products as applied by homeowners, which is expected to be in a much more concentrated form than atrazine dissolved in shower water after being diffused and dissipated in the environment. These estimates show that dermal exposures are greater than inhalation exposures for atrazine. Before risk mitigation, dermal exposures from use of atrazine products in and around the home are estimated to be 1.6 to 0.0034 mg/kg/day. Inhalation exposures for atrazine (0.00023 and 0.00002 mg/kg/day) are 3 to 4 orders of magnitude lower than dermal exposures to liquid formulations (0.16 to 0.0034 mg/kg/day). Therefore, HED expects inhalation exposure to be insignificant relative to oral and dermal exposures. Given the conservative assumptions resulting in high-end estimates for the dermal and inhalation exposures used in the aggregate risk assessments, and the belief that exposure to atrazine through showering and swimming will be insignificant in comparison, HED believes any potential exposures through showering and swimming have been adequately covered. Finally, HED believes that the 1000-fold uncertainty factor used for dietary exposure and the 300-fold uncertainty factor used for residential exposure used in conjunction with the conservative assumptions regarding residential exposure used in the atrazine human health risk assessment is adequately protective of aggregate exposures to atrazine.

American Water Works Association (AWWA):

The AWWA in association with Dr. Douglas Crawford-Brown of UNC and McGuire Environmental Consultants, Inc. submitted comments on the human health risk assessment. These comments and HED responses are summarized below. In general, they request clarification on how the common mechanism of toxicity and the risk assessment will affect regulatory development in OPP and OW. AWWA expresses concern that the risk assessment has underestimated the number of CWS "at risk". They request clarification on the rationale underlying the application of the 10X FQPA safety factor, citing their belief that at most a 3X is warranted. They cite a number of data needs, including: treatment and analytical methodologies and occurrence data for the chlorinated degradates, and reliably predicting 90-day average concentrations. They provide several mitigation proposals.

<u>Comment</u>
Common Mechanism of Toxicity - AWWA and consultants request clarification on how the common mechanism of toxicity and the risk assessment will affect regulatory development in OPP and OW.

<u>HED Response</u>
HED cannot comment on how the common mechanism of toxicity for the triazines will affect OPP or OW regulations regarding this class of pesticides until the OPP has completed the cumulative risk assessment for the triazines sharing a common mechanism of toxicity. Regulatory developments based on the atrazine risk assessment are in process, and stakeholder meetings will be held to ensure involvement of stakeholders in the process. As to any specific regulatory actions, HED must defer to SRRD.

<u>Comment</u>
CWS @ Risk - AWWA expresses concern that the risk assessment has underestimated the number of CWS "at risk".

<u>HED Response</u>
HED believes the CWS identified in the risk assessment represent the high end of exposures to atrazine and the chlorinated degradates; however, HED agrees with the AWWA in that the risk assessment probably did not identify all CWS "at risk". There are several reasons for this of which the most obvious is the limited database used in the assessment. Although the drinking water monitoring database for atrazine is the most complete for any pesticide to date, it is still lacking regarding degradates for which very limited data were available, and the frequency of sampling under the SDWA. Also of concern is the sporadic pattern with which concentrations of concern occur at CWS. Even if a CWS has no exposures of concern for several years, it does not necessarily mean that it never will. HED believes that a continuing process to identify CWS @ risk now and in the future, and that continued monitoring at CWS identified as of potential concern is a necessary part of any mitigation plan. The OW is currently assessing the available

databases for atrazine in drinking water statistically to estimate the extent of exposures of concern (i.e., the total number of CWS with 90-day average concentrations likely to exceed > 12.5 ppb). HED defers to OW for details on the results of this assessment.

Comment

FQPA Safety Factor (SF) - AWWA notes that the rationale for the 10X FQPA SF is not clear and states that a 3X would have been sufficient. HED provides the following clarification as to why a 10X FQPA safety factor was applied to dietary risk assessments. The rationale can also be found in the April 2002 FQPA and HIARC memoranda posted to the atrazine website.

HED Response

FQPA directs EPA to use an additional 10-fold safety factor in assessing risks to infants and children to take into account the potential for pre- and post-natal toxicity and the completeness of the toxicity and exposure databases. The default 10X factor can only be reduced if the different margin of safety based on reliable data would be safe for infants and children. This is referred to as the FQPA safety factor provision. Under this provision OPP used a weight-of-evidence approach wherein all data on toxicity and exposure are considered together for atrazine. Under this approach, the level of confidence associated with the hazard and exposure assessments and any residual uncertainties regarding either toxicity or exposure are evaluated. The 10X FQPA safety factor was applied to dietary risk assessments for atrazine based on residual uncertainties regarding atrazine's toxicity and the extent of exposure to atrazine and the chlorotriazines.

Specifically, the HIARC (HED's Hazard Identification Assessment and Review Committee) determined that the toxicity database was complete and there was evidence of increased qualitative susceptibility of the young following exposure to atrazine in the rabbit developmental study. The HIARC then performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual concerns after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual concerns are identified, HIARC examines whether these residual concerns can be addressed by a special FQPA safety factor and, if so, the size of the factor needed.
For atrazine, the HIARC concluded that there is low degree of concern for the qualitative increased susceptibility (increased fetal resorptions at a dose level that resulted in decreased body-weight gain and clinical signs in the maternal animal) because: 1) the NOAELs in the study are well characterized; and 2.) the fetal effects seen occurred at a high dose level (75 mg/kg/day). The HIARC also concluded that there are no residual concerns for these effects considering that the Acute RfD established for Atrazine/DACT is based on a NOAEL of 10 mg/kg which is

protective of the fetal effects observed at 75 mg/kg/day in the developmental rabbit study.

After considering the effects observed in the special developmental studies with atrazine in the context of establishing toxicity endpoints for risk assessment, the HIARC identified the following residual concerns:

> "*Since the focus of the testing with Atrazine in the young rat has been limited to short periods of dosing to specific developmental periods, uncertainties are raised for susceptibility during earlier developmental periods as well as for consequences of earlier developmental exposure with longer duration of dosing throughout development. The effects of neurotransmitters/peptides (known to be critical for normal development and which could potentially translate into severe effects in children that may not be manifested until later in life) have not been fully characterized. And as the FIFRA Scientific Advisory Panel noted, there are concerns for behavioral effects in the young resulting from Atrazine's CNS mode of action and the dose level at which these effects might occur compared to reproductive/developmental effects[1].*"

Considering the existing data used for toxicity endpoint selection, the HIARC used the following rationale to conclude that an additional Special FQPA Safety Factor of 3X would be adequate to account for these hazard-based (toxicity) residual uncertainties described above:

"*The toxicology endpoints selected for risk assessment are all consistent with Atrazine's mode of toxicity using the most sensitive endpoint with the lowest NOAEL (1.8 mg/kg/day). When comparing the effects observed in adults to those observed in the young, the HIARC considered the results of the pubertal assay. It is noted that delayed puberty was observed in both male and female offspring exposed to Atrazine during the pubertal period (30 days for the males and 20 days for the females) and that clear NOAELs were established for this endpoint in both sexes (6.25 mg/kg/day in males; 12.5 mg/kg/day in females). If the lowest offspring NOAEL from this study is protected by a factor of 3X, the extrapolated NOAEL is 2 mg/kg/day. Comparing this value to the adult NOAEL of 1.8 mg/kg/day from the 6-month LH Surge study (used to establish the Chronic RfD and for the intermediate and chronic oral, dermal, and inhalation exposure*

[1]SAP Report No. 2000-05; Atrazine: Hazard and Dose Response Assessment and Characterization. "Because of the rapid developmental brain changes...the influence of Atrazine on neurotransmitters in the hypothalamus and on GnRH may well have a differential, permanent effect on children. This phenomenon is the basis of the relatively new field of behavioral teratology. Atrazine could influence the migration of cells and the connectivity of the CNS. The influence of Atrazine on the hypothalamus and on GnRH may have a differential effect on children. This effect could be latent, and emerge later during the challenge of puberty, or during senescence. Behavioral alterations may be the most sensitive outcome. This possibility should be addressed...."

scenarios) indicates that the young are not likely to be an order of magnitude more sensitive than the adult. Therefore, the HIARC concluded that a half-log reduction in the default Special FQPA Safety Factor is considered to be sufficiently protective of the concerns for this CNS mode of action in the young."

Once the HIARC makes its determination as to the necessary "hazard-based" (toxicity) FQPA safety factor, the FQPA Safety Factor Committee (FQPA SFC) determined the overall FQPA SF by considering the HIARC's determination and evaluation regarding increased susceptibility/sensitivity, degree of concern analysis, completeness of the toxicity database, and any residual hazard-based uncertainties in conjunction with the completeness of the exposure database, and any residual uncertainties associated with the exposure database and the exposure assessments based on it.

After careful deliberation, the FQPA SFC "concluded that, as to dietary risk, the default 10X FQPA safety factor is statutorily required because of the absence of reliable evidence showing that an additional safety factor different than the statutory 10X default would be protective of infants and children. The principal grounds for this conclusion are: 1.) the HIARC identified residual concerns for the effects of the neuroendocrine mode of action described for Atrazine on the development of the young (Refer to Section I.3.B.). These concerns could not be accounted for in the determination of toxicity endpoints and traditional uncertainty factors to be used in risk assessment; and 2.) residual concerns were also identified with regard to the drinking water exposure assessment. The various water monitoring data sources which exist for Atrazine and its chlorinated metabolites indicate that exposure via drinking water sources is high in some of the systems that have been monitored and widespread low levels are commonly detected. Although it is known that there is significant, widespread exposure to Atrazine and its metabolites in drinking water, limitations in the extent, frequency, and compounds tested for in the monitoring data raise significant uncertainties regarding the level of exposure to Atrazine and its metabolites. Because of these uncertainties, the Committee concluded there is not reliable data to assign an additional safety factor that would adequately protect the safety of children by insuring that exposure in drinking water is not underestimated. The FQPA specifies that in the absence of such reliable data a default value of 10X is to be used as an additional safety factor for the protection of infants and children. As discussed below, the Committee believes there is reliable data to address the residual uncertainties regarding the neuroendocrine mode of action; however, because reliable data is not available as to all of the issues raising residual uncertainties, use of the default 10X factor is appropriate."

Comment

Data Needs - Treatment technologies, and analytical methodologies, occurrence data and the frequency of monitoring for atrazine and the chlorinated degradates.

HED Response

The data needs listed are mostly under the purview of the OW and HED defers to OW regarding treatment technologies, and analytical methodologies for chlorinated metabolites of atrazine in drinking water. HED must also defer to OW regarding occurrence data and the frequency of monitoring for atrazine and the chlorinated degradates in a way that will adequately capture 90-day average concentrations of concern under any compliance monitoring scheme. However, weekly to biweekly monitoring during application season were used for the VMS and ARP databases, and appear adequate to capture the seasonal pulses (spikes) in atrazine concentrations otherwise missed with the quarterly sampling schemes currently used under the SDWA.

Comment

Mitigation Options - AWWA included a section discussing options to mitigate the risk from atrazine use including use restrictions, best management practices, use bans in certain watersheds, a complete ban on use, and several programs to defer the costs of atrazine contamination of water to the registrant.

HED Response

OPP is currently working on mitigation strategies and is including AWWA in these discussions as a stakeholder. During these meetings, AWWA should have ample opportunity to discuss their suggestions and concerns regarding mitigation options.

AWWA Consultants (Dr. Douglas Crawford-Brown and McGuire Environmental, Inc.):
Dr. Douglas Crawford-Brown stated that overall the risk assessment document presented a reasonable set of conservative calculations for assessing exposures to atrazine and the chlorinated metabolites in food, water, and residential settings. He further noted that a reasonable set of toxic endpoints were selected and correctly used to establish reference doses. The conclusions of the document were generally reasonable and well documented. He offers the following comments:

Comment

Probabilistic component of acute exposures - Dr Crawford-Brown notes that in the acute assessment for food exposures, food intake and body weight are correlated for each individual considered in the assessment. These data come from records contained in the Continuing Survey of Food Intake by Individuals (CSFII), and are used as distributions representing an individual's daily food intake/body weight on a single day. He also notes that to estimate acute drinking water exposures in a single day, drinking water intake and body weights are not correlated for individuals.

<u>HED Response</u>
HED agrees with the comment that data on body weight and drinking water consumption linked are available and should be used. However, HED used a different approach in assessing acute food versus drinking water exposures. The acute food exposure assessment was conducted probabilistically using distributions of individuals' food intake linked to their reported body weights along with distributions of food residues, while the acute drinking water exposure assessment used a screening-level approach. The screening-level approach assumes default body weights and consumption values currently in use by the OW in setting drinking water standards rather than body weight/consumption values from the CSFII or the Exposure Factors Handbook. Under the acute assessment, the simpler screening-level approach for drinking water indicated that acute risks through drinking water were below levels of concern, and therefore, more refined probabilistic assessments for acute exposures in drinking water were not needed. However, for CWS showing intermediate-term risks of concern under the screening-level approach, probabilistic drinking water exposure assessments were conducted using distributions of linked body weight and consumption per individual.

<u>Comment</u>
FQPA Safety Factor - The application of the 10X FQPA safety factor is not explained satisfactorily.

<u>HED Response</u>
See response under FQPA Safety Factor above.

HIARC and FQPA documents can be found at the following URLs:

http://www.epa.gov/oppsrrd1/reregistration/atrazine/hed_fqpasfreport_8apr02.pdf

http://www.epa.gov/oppsrrd1/reregistration/atrazine/hed_hiarc_atrazine_5april02.PDF

<u>Comment</u>
Document organization and clarity - The PAD should be explained earlier in the document.

<u>HED Response</u>
HED acknowledges that the programs use of varying terms as risk metrics is confusing and should be explained early and often.

Comment

The document needs an example of how quarterly average concentrations were calculated.

HED Response

HED initially calculated simple arithmetic quarterly average concentrations of chlorotriazines for those CWS in VMS and ARP. Typically these CWS may have had a total of 30 samples per year, and up to 10-12 samples in the spring quarter. Samples within a given quarter tended to be evenly spaced in time, but not exactly. Therefore, time-weighted mean concentrations (TWMC) were calculated and compared to the simple arithmetic values.

The TWMC was calculated by the following:

$$TWMC = (C_1 \times T_1 / T_T) + (C_2 \times T_2 / T_T) + (C_3 \times T_3 / T_T) \ldots\ldots\ldots\ldots\ldots (C_n \times T_n / T_T)$$

where, C_1 is concentration value in the first time period of interest (weekly sample), T_1 is the first time period of interest (7 days), and T_T is the total time period of interest (90 days).

Comment

The document should explain the equations and assumptions used to estimate the chlorinated degradates in exposure assessments.

HED Response

The details of this process are quite lengthy and involved. Consequently, to keep the length of the risk assessment document down, the details are contained in supporting documents. The equations used to estimate the chlorinated degradates in drinking water are contained in the EFED chapter dated October 16, 2000, "Drinking water exposure assessment for atrazine and various chlorotriazine and hydroxy triazine degradates", H. Nelson, J. Lin, M. Frankenberry, posted to the website under Preliminary Risk Assessment at the following URL: http://www.epa.gov/oppsrrd1/reregistration/atrazine/drinkingwater.pdf

The chlorinated degradates were estimated in food based on field trial studies and plant and animal metabolism studies. Foods were analyzed for atrazine and the chlorinated degradates in these studies. The details are contained in the document dated January 18, 2000, "Atrazine. Anticipated Residues and Acute and Chronic Dietary Exposure Assessments for Atrazine ", D. Soderberg, C. Eiden, posted to the website under Preliminary Risk Assessment at the following URL: http://www.epa.gov/oppsrrd1/reregistration/atrazine/antici_residues.pdf

Comment

Parameters regarding the residential risks for children were not clear in the text of the document, but contained in tables.

HED Response

Again, the reader is referred to the supporting documents on the website for details. All equations and assumptions are clearly spelled out but excluded from the risk assessment because of length considerations. The document can be found at the following URL: http://www.epa.gov/oppsrrd1/reregistration/atrazine/hed_ore_25april02.pdf.

Comment

Carcinogenic Potential of Atrazine - The document only briefly discusses atrazine's cancer classification, more is needed. A discussion of the MCL versus the 12.5 ppb figure used in the document.

HED Response

The cancer issue was brought before a SAP in June 2000. The details of that assessment are also quite lengthy and discussed only briefly in the risk assessment in the interest of brevity. For those interested in the details the reader is referred to the following website: May 22, 2000 document atrazine to the FIFRA Scientific Advisory Panel (SAP) (see Part A,http://www.epa.gov/scipoly/sap/2000/june27/finalparta_atz.pdf and Part B, http://www.epa.gov/scipoly/sap/2000/june27/finalpartb_atz.pdf). Please see the response to NRDC's comment on the MCL versus the 12.5 ppb DWLOC on p. 8.

Comment

Uncertainty - Dr. Crawford-Brown correctly notes that the discussions around the titles of "Uncertainty" are not quantitative and are more correctly called discussions of levels of confidence.

HED Response

HED agrees with this comment.

Comment

Probabilistic assessments - They are not clearly explained in the risk assessment document. The reader cannot determine the underlying probability distributions, the quality of the distributions, how samples were selected......etc. Dr. Crawford-Brown expresses concern that the distributions are not representative but biased towards sites with atrazine. McGuire Environmental, Inc. consultants also expressed concern that the data used were inappropriate for a national assessment.

HED Response

HED can refer the reader to Appendix III of the revised risk assessment, and the memorandum entitled, "Review of Probabilistic Exposure Assessment for Drinking Water from 28 community Water Systems, dated April 23, 2002, C. Eiden, posted to the website under Revised Risk Assessment at the following URL:

http://www.epa.gov/oppsrrd1/reregistration/atrazine/probabilisticreview_23apr02.pdf.

Although the actual distributions of water concentrations are not given there, the methodology used to create them is described in some detail. The document refers to submitted probabilistic assessments conducted by Novigen Sciences, Inc. using the Calandex™ model, and methodology and procedures approved by OPP and used for the cumulative risk assessment for the organophosphate pesticides. If need be the actual distributions of drinking water intake and body weight are available from the CSFII, and the actual distributions of water concentrations may be requested under the FOIA.

The concern regarding the representativeness of the probabilistic exposure assessments correctly notes that the data used to develop the water concentration distributions used are from CWS with high atrazine exposures and the data set is itself conservatively biased. However, it should be noted that the probabilistic assessments were conducted for specific CWS only, therefore, this is not a problem. Had the results of the risk assessment been extrapolated from these CWS with high-end exposures to the entire US population, then the concern would have been well-founded. However, as stated in the risk assessment document, the probabilistic assessments were conducted for a small number of CWS ~30 for which screening-level assessments indicated risk of concern, and for which enough high quality monitoring data were available to conduct a probabilistic exposure assessments. A separate probabilistic assessment was conducted for each of the ~30 CWS. The results were not extrapolated beyond the specific CWS for which they are representative.

The risk assessment did not attempt to conduct a national assessment because of the lack of data, i.e., roughly 33-40% of the CWS using surface water in the US have data on atrazine. Screening-level assessments were conducted with the available data for these CWS, only, and probabilistic assessments only for those CWS with risk of concern based on the screen. In effect, the risk assessment included only those CWS with data on atrazine, and was indeed a biased assessment looking at high-end exposures only. The remaining 60+% of CWS using surface water in the US either do not collect data on atrazine because of lack of use or detection under the SDWA waiver program. The risk for these CWS could be assumed to be zero, but the risk assessment document did not conclude that because of a lack of verification that the data waivers were current and appropriate. Prompted by comments from the NRDC, OPP has been in discussion with the OW about the waiver program.

<u>Comment</u>

DWLOC Issues - How should the reader interpret the results on residential exposures and their effect on the DWLOC? Is it suggested that the DWLOC be reduced for policy purposes?

<u>HED Response</u>

Under OPP's aggregate screening-level exposure assessment, the DWLOC value varies according to what is left over in the risk cup once estimates of food and residential exposures (if warranted) are considered. DWLOC values vary with risk assessment type, i.e., acute, short-term, intermediate-term, and chronic) as each risk assessment varies by toxic endpoints, uncertainty factors, food and residential exposures. Consequently, under any given exposure scenario the greater the exposure through food and residential uses the lower the DWLOC values will be. The DWLOC is not a standard but a way of measuring aggregate risk in the form of a theoretical upper limit on what is allowable in drinking water in light of other exposures. The DWLOC is simply based on the portion of the allowable exposure (NOAEL/UF or PAD) left after subtracting food and residential exposures. The relationship of the PAD to the DWLOC is directly proportional. The reader is referred to the following URL for details: http://www.epa.gov/pesticides/trac/science/screeningsop.pdf

HED first estimates dietary and residential exposures separately, and then in aggregate. If the residential exposure is above levels of concern independent of the food or water exposures, then by default, the DWLOC value for the residential exposure scenario exceeding levels of concern is zero, i.e., because there is an exposure pathway by itself exceeding levels of concern, there is no room for aggregate exposures through water and food. For any individual residential exposure scenario with risk estimates of concern, an aggregate exposure assessment in theory is not possible. It is HED policy that when residential exposure scenarios exceed levels of concern, the DWLOC value is set at zero indicating no more room in the risk cup until that residential exposure is mitigated.

In the case of atrazine, OPP does not anticipate intermediate-term exposures to atrazine in residential settings because of residential uses. Residential exposures do not impact the intermediate-term DWLOC value at all. Therefore, the aggregate exposure assessment for intermediate-term exposures only includes exposures through food and drinking water as these are the pathways contributing the most to exposure to atrazine and the chlorinated degradates with reliable, available data. Under the aggregate intermediate-term exposure assessment (90 days), the lowest DWLOC of concern is 12.5 ppb for infants and is based on a NOAEL of 1.8

mg/kg/day, a 1000-fold uncertainty factor, and chronic food exposures of 0.000008 mg/kg/day.

However, OPP does anticipate short-term exposures to atrazine in residential settings because of residential uses. Residential exposures do impact the DWLOC value. Therefore, the aggregate exposure assessment for short-term exposures includes exposures through food, drinking water, and residential uses as these are the pathways contributing the most to exposure to atrazine and the chlorinated degradates with reliable, available data. Under the short-term drinking water exposure assessment, the lowest DWLOC of concern is zero for toddlers based on short-term exposures (<30 days), a NOAEL of 6.25 mg/kg/day and a 300-fold uncertainty factor, chronic food exposures of 0.000008 mg/kg/day, and high-end residential exposures. A DWLOC of zero simply indicates that short-term exposure through the residential pathway **alone** exceeds the level of concern.

For example, the DWLOC values for intermediate-term and chronic exposures are less than the DWLOC values for short-term exposures even though aggregate short-term exposures include food, water, and high-end residential exposures while the aggregate intermediate-term and chronic exposures include food and water only because intermediate-term and chronic residential exposures are not anticipated. This is largely because the short-term exposure scenarios are based on and driven by an endpoint of 6.25 mg/kg/day and an UF of 300, whereas the intermediate-term and chronic exposure scenarios are based on an endpoint of 1.8 mg/kg/day and an UF of 1000. The greater the endpoint and lower the UFs, the greater the allowable dose upon which the DWLOC is based. Again, the DWLOC is directly proportional to the endpoint and UFs.

Comment

Tolerance Reassessment Impacts on Water Quality - Dr. Crawford-Brown expresses concern that increases in tolerances may lead to a situation where increased tolerances lead to higher allowable levels of atrazine in drinking water under the aggregate risk assessment.

HED Response

Increases in tolerances do not translate directly into increases in allowable exposure to a given pesticide. The tolerance represents a legal limit on a pesticide residue that may be on a given crop that has been treated at the maximum labeled rate and harvested at the shortest post-harvest interval. That is, the tolerance represents the maximum residue expected at the farm gate prior to any storage and processing, which may include washing, peeling, and cooking. The tolerance's main function is to control for any illegal/misuse of a pesticide product on a crop as the crop moves through the channels of commerce. The tolerance does not represent the pesticide residues expected (anticipated) on foods that humans or animals eat. Although tolerance level residues may be used in dietary risk assessments, these assessments are considered crude and for more refined assessments OPP uses monitoring data collected on crops and foods closer to the point of consumption for exposure and risk assessment purposes. The allowable dose of atrazine and the chlorinated degradates in food, drinking water, and the home under an aggregate risk assessment is based on the chronic PAD (0.0018 mg/kg/day) or acute PAD (0.01 mg/kg/day) that has no relationship to the actual tolerance.

In the case of atrazine, the tolerances were increased for several commodities including meats and milk. This increase is a reflection of the addition of the chlorinated degradates of atrazine in the tolerance expression, not any increase in the allowable dose of atrazine and the chlorinated degradates. It means the legal limit for atrazine must now include its three degradates, as well, and that USDA and FDA should be monitoring for all the degradates as well as the parent. Most tolerances for atrazine on crops were decreased because of decreases in the use rates of atrazine on grains such as corn and sorghum.

New York and Connecticut State Attorney General's Offices (NYSAGO):

Comment

The revised human health risk assessment fails to assess adequately the endocrine disruption, reproductive, and carcinogenic effects of atrazine.

HED Response

HED disagrees with the NYSAGO's comment. Atrazine is one of the best studied pesticides with an extensive data base on its mechanism of toxicity. The perturbation of the hypothalamic-pituitary-gonadal axis is the primary and only established mode of action for atrazine. The June 2000 SAP agreed with this conclusion. As part of the cancer mode of action evaluation, however, EPA fully considered other modes of action, and included discussion of these alternative pathways in its May 22, 2000 document atrazine to the FIFRA Scientific Advisory Panel (SAP) (see Part A,http://www.epa.gov/scipoly/sap/2000/june27/finalparta_atz.pdf and Part B, http://www.epa.gov/scipoly/sap/2000/june27/finalpartb_atz.pdf). Furthermore, EPA asked the June 27, 2000 FIFRA SAP "Have other modes of carcinogenic action been sufficiently discussed and ruled out?". The SAP concluded that "Alternative modes of action have been thoroughly discussed and ruled out." in the May 2000 EPA document. Below are more specific responses to the other mechanistic pathways raised by NRDC. The Scientific Advisory Panel (SAP) report convened in June of 2000 and all of the supporting documentation that went into that SAP are available for review at the above website. Also see response to NRDC comment on pages 13 - 14.

As to reproductive and developmental effects, HED based all aspects of the human health risk assessment on either reproductive or developmental effects, i.e., the acute risk assessment was based on delayed ossification and prostatitis effects in fetuses and developing offspring, respectively; the short-term risk assessment was based on pubertal delays; the intermediate-term and chronic risk assessments were based on disruptions to the estrus cycle and hormone-mediated ovulation effects. In addition, the 10X FQPA SF was based in part on the uncertainties surrounding the critical periods of development in the young versus the timing of atrazine administration. The following excerpt is taken from the HIARC document for atrazine (April 5, 2002). It provides the basis for the rationale as to why residual uncertainties regarding atrazine's toxicity with regards to developmental consequences in the young exist. (Also see response on page 31.)

> "*Since the focus of the testing with Atrazine in the young rat has been limited to short periods of dosing to specific developmental periods, uncertainties are raised for susceptibility during earlier developmental periods as well as for consequences of earlier developmental exposure with longer duration of dosing throughout development. The effects of neurotransmitters/peptides (known to be critical for normal development and which could potentially translate into severe effects in children that may not be manifested until later in life) have not been fully characterized. And as the FIFRA Scientific Advisory Panel noted, there are concerns for behavioral effects in the young resulting from Atrazine's CNS mode of action and the dose level at which these effects might occur compared to reproductive/developmental effects*[2]."

The NYSAGO's comment that the risk assessment states, "...there was no evidence of increased sensitivity following exposure to atrazine", with respect to NHEERL studies is correct. The statement in the risk assessment should have been clearer by stating, "....there was no evidence of increased "quantitative" sensitivity following exposure to atrazine", with respect to NHEERL studies. [The specifics are given in the HIARC and FQPA memoranda previously cited.] The endpoints (LOAELs) at which these pubertal (endocrine) effects from the NHEERL studies were seen in young rats were greater than or equal to 12.5 mg/kg/day and were all above the lowest endpoint (LOAEL) identified for endocrine effects in the adult rat (3.65 mg/kg/day) indicating no increased quantitative sensitivity. However, the HIARC document actually states the following

[2]SAP Report No. 2000-05; Atrazine: Hazard and Dose Response Assessment and Characterization. "Because of the rapid developmental brain changes...the influence of Atrazine on neurotransmitters in the hypothalamus and on GnRH may well have a differential, permanent effect on children. This phenomenon is the basis of the relatively new field of behavioral teratology. Atrazine could influence the migration of cells and the connectivity of the CNS. The influence of Atrazine on the hypothalamus and on GnRH may have a differential effect on children. This effect could be latent, and emerge later during the challenge of puberty, or during senescence. Behavioral alterations may be the most sensitive outcome. This possibility should be addressed...."

regarding sensitivity of the young to atrazine exposure of which only a portion was captured in the risk assessment:

"The HIARC concluded that there is a concern for pre- and/or postnatal toxicity resulting from exposure to Atrazine.

Determination of Susceptibility

The HIARC concluded that there was no increased quantitative or qualitative susceptibility in any of the guideline studies on atrazine in the rat, and there was no increased quantitative susceptibility in the rabbit study. However, there was increased qualitative susceptibility in the rabbit study [increased resorptions (deaths) at a dose level that resulted in decreased body-weight gain and clinical signs in the maternal animal]. There are other non-guideline studies on atrazine that show evidence of endocrine disruption [prostatitis study, delayed puberty study, and data on LH surge attenuation, and estrous cycle alterations]. The primary underlying events that lead to mammary and pituitary tumor formation following atrazine exposure of Sprague-Dawley female rats involve disruption of the hypothalamic-pituitary-ovarian axis. Since aspects related to this axis are involved in reproductive and developmental competency, there is a concern for adverse reproductive and developmental effects in maternal animals and their offspring. Several special studies have been performed that show that treatment of pregnant rats with atrazine can lead to reproductive and developmental effects that may be associated with endocrine alterations. Additionally, the neurotoxicity seen in the non-guideline studies with atrazine is a central nervous system (CNS) toxicity - specifically, neurotransmitter and neuropeptide alterations at the level of the hypothalamus.

Studies in the open literature indicate increased qualitative susceptibility. Dosing of dams immediately following parturition [postnatal days 1-4] resulted in prostatitis in male offspring, and dosing of the young following weaning resulted in delayed puberty in both sexes. The mode of action for these two effects (prostate inflammation and delayed puberty) is believed to be similar to the mode of action described for atrazine-associated cancer and involves the CNS neuroendocrine alterations, specifically, neuroendocrine alterations at the hypothalamus.

In the previous HIARC assessment of DACT, it was determined that increased quantitative susceptibility of the young was observed in the rat developmental toxicity study on DACT. A re-examination of the maternal body-weight gain data from that study was performed subsequently, and it was determined that decreased body-weight gain was evident during the initial dosing period [gestation days 6-8] at 25 mg/kg/day, and the magnitude of the decrease [32%] is considered to be evidence of maternal toxicity. Therefore, the NOAEL *for maternal toxicity has been changed to 2.5 mg/kg/day, and the LOAEL for maternal toxicity is 25 mg/kg/day. The developmental NOAEL was 2.5 mg/kg/day based on increase incidences of incompletely ossified parietals, interparietals and unossified hyoids at 25 mg/kg/day (LOAEL). Therefore, developmental toxicity and maternal toxicity occurred at the same dose level [25 mg/kg/day], and there is no apparent increased quantitative susceptibility following DACT exposure in this study. Additionally, it was determined that a 2-generation reproduction study on DACT is not required.*

Degree of Concern Analysis and Residual Uncertainties

Since there is evidence of increased susceptibility of the young following exposure to Atrazine in the rabbit developmental study and in several special studies conducted to evaluate endocrine effects, HIARC performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual concerns after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual concerns are identified, HIARC examines whether these residual concerns can be addressed by a special FQPA safety factor and, if so, the size of the factor needed. The results of the HIARC Degree of Concern analyses for Atrazine (and DACT) follow.

Prenatal Developmental Study with Atrazine in Rabbits

The HIARC concluded that there is low concern for the qualitative increased susceptibility (increased fetal resorptions at a dose level that resulted in decreased body-weight gain and clinical signs in the maternal animal) because: 1) the NOAELs in the study are well characterized; and 2.) the fetal effects seen occurred at a high dose level (75 mg/kg/day).

The HIARC also concluded that there are no residual concerns for these effects considering that the Acute RfD established for Atrazine/DACT is based on a NOAEL of 10 mg/kg which is protective of the fetal effects observed at 75 mg/kg/day in the developmental rabbit study."

It is fair to say that this distinction between quantitative and qualitative sensitivity could have been made clearer and captured more fully in the risk assessment. It is reasonable to say that all aspects of atrazine's toxicity have neither been fully studied nor understood. However, these residual uncertainties surrounding atrazine's toxic effects on development and reproductive consequences for the young were clearly considered and ultimately formed the basis for maintaining the full 10X FQPA SF along with residual uncertainties regarding exposure.

The portions of the comment referring to the endocrine effects in frogs has not been fully explored at this time as those results were just emerging at the time of the atrazine public technical briefing. HED must defer to the Environmental Fate and Effects Division (EFED) as to the validity of these emerging findings. EPA expects to convene a Scientific Advisory Panel in the Summer 2003 to discuss the frog issue.

<u>Comment</u>
Pesticides in general, and atrazine in particular occur widely in surface and drinking water. The risk assessment fails to include an analysis of the aggregate risk posed by atrazine and its metabolites, as well as an analysis of multiple pesticides in drinking water. The human health risk assessment does not adequately consider exposures to atrazine through drinking water and air.

<u>HED Response</u>
HED agrees with the case made by the NYSAGO that atrazine contamination in US surface waters is widespread as seen from the USGS' variety of databases on water quality. Atrazine is present in surface waters in the US typically at low levels between 0.1 and 1 ppb. However, the kinds of data collected by the USGS to determine the quality of US waters, i.e., raw water in streams, lakes, creeks, rivers, ditches is applicable to ecological risk assessments rather than risk assessments for human health. These data do not represent pesticide concentrations in raw water at intake points into drinking water facilities but may be miles upstream, and consequently do not reflect the influence of dilution, treatment, and distribution effects within the treatment facility that all may affect pesticide concentrations in finished drinking water. These data were used appropriately by OPP in the ecological risk assessment, but should not be used in human health assessments. OPP's human health risk assessments are necessarily health-based, quantitative, and linked to a toxic endpoint for health effects rather than qualitative and based on general occurrence information.

OPP's human health risk assessment was based on finished drinking water from a variety of sources including compliance monitoring under the SDWA and more intensive monitoring programs of drinking water in CWS in areas with known high use of and exposures to atrazine. The data used reflect a database biased towards CWS with atrazine exposure. The exposure assessment considered each of ~4000 CWS using surface water with data on atrazine serving 55 million + people and representing ~40% of all CWS in the US using surface water, and is believed to reflect all CWS reporting data on atrazine. Data on 418 CWS using groundwater (50% of which were the CWS using groundwater with prior detections of atrazine reported under the SDWA) representing 14,115 CWSs serving 20.5 million people were assessed. In addition to these data sets, 2 programs of intensive monitoring in CWS using surface water were used to estimate 90-day average exposures. One program included ~ 100 CWS and the other ~ 175 CWS. These CWS are believed to contain CWS with exposures to atrazine and the chlorinated metabolites that represent high-end exposures. Although incomplete, these data sets represent the most robust data set for a pesticide in finished drinking water. OPP intentionally conducted a drinking water assessment using targeted monitoring data CWS by CWS in the interest of identifying specific CWS at risk. Although it is unlikely that all CWS with high atrazine exposures were identified, this assessment is believed to highlight not the entire extent of exposure but the likely high-end of exposures. The OW is currently assessing the extent of these high-end exposures.

HED agrees that the metabolites are formed and exposures to them must be included in the risk assessments. However, HED disagrees with the statement that the risk assessment fails to include aggregate exposures to atrazine and its metabolites. The human health risk assessment for atrazine included estimates of exposures to atrazine, desethyl atrazine (DEA), des isopropyl atrazine (DIA), and diaminochlorotriazine (DACT) in food and drinking water. These four compounds are considered to have a common mechanism of toxicity and believed to have equivalent toxicity to the parent compound. A separate assessment for the hydroxy metabolites was also included in the risk assessment Exposure to the hydroxy metabolites were not aggregated with the exposure to atrazine and the chlorinated metabolites, as the hydroxy compounds are not believed to share a common mechanism of toxicity with the chlorotriazine compounds.

Concern was expressed that the real exposure to humans in the diet cannot be ignored. The details of the dietary assessments for atrazine and the chlorinated metabolites, as well as, the hydroxy atrazine dietary assessment showing that dietary (food) exposures to chlorotriazines and hydroxy metabolites are insignificant (<1% of the a PAD and cPADs) can be found at the following URL: http://www.epa.gov/oppsrrd1/reregistration/atrazine/antici_residues.pdf.

The comment expresses concern that the risk assessment did not include atmospheric deposition contributions to exposure or multiple pesticide exposures in the risk assessment. Because HED used monitoring data for surface water, the contribution of atrazine to water supplies as deposited by atmospheric transport and rain is captured, i.e., is inherent in the database. There was no need to estimate this contribution from drift with computer models, etc. Any contribution to the dietary exposure from rainwater is also reflected in the monitoring data used to assess dietary exposures. For a further discussion of atrazine in rain water and fog and multiple pesticides see <u>HED Response</u> to Dr. John Wargo on these issues on pp. 48 - 49. As to the chemical mixtures issue, HED acknowledges that pesticides co-occur, but OPP has no statutory authority to regulate or methodology to assess risks associated with chemical mixtures not based on a common mechanism of toxicity. OPP will conduct a risk assessment in the future for triazines with a common mechanism of toxicity.

Comment

The human health risk assessment improperly applies a 3-fold uncertainty factor under the FQPA for residential exposures. The use of a 3-fold safety factor for residential exposures is wholly unjustified given the uncertainties associated with exposure.

HED Response

The following excerpt is from the FQPA SFC memorandum dated April 8, 2002.

> *"The FQPA Safety Factor Committee concluded that an additional Special FQPA safety factor of 3X is adequate for assessing residential exposures to Atrazine / DACT because the concerns for drinking water (described above) would have little or no impact on the residential exposure scenarios. The concerns for the effect of the neuroendocrine mode of action on the development of the young remain and the Committee concluded that there are reliable data to address these concerns through use of an additional Special FQPA Safety Factor of 3X (Refer to Section I.3.B for the rationale that this factor would be adequate to account for these hazard-based residual uncertainties)."*

In considering residential exposures under FQPA, the SFC determined that although there are residual hazard-based uncertainties for atrazine that apply to the young, residual concerns for exposure uncertainties would be adequately covered by the 3X SF for hazard-based concerns because of the conservative assumptions used to estimate children's residential exposure. These assumptions are based on the OPP's Standard Operating Procedures for Residential Exposure (revised 2001), and can be reviewed in HED's occupational residential exposure chapter for the reregistration eligibility decision.

The risk estimates for residential exposures are considered to be conservative. A variety of data were used to estimate exposures, some of it chemical-specific for atrazine. Residential handler exposure and risk estimates were conducted using two sets of surrogate chemical data: the Occupational and Residential Exposure Task Force (ORETF) study data and the Residential Standard Operating Procedures (SOPs). Generally, the Residential SOP data (default assumptions) are more conservative than ORETF data. Both data sets show wide variations in exposure depending on individual behaviors. Dermal postapplication exposures to atrazine were based on the higher average daily residues from the chemical-specific turf transferable residues (TTR) study data, but also used standard assumptions for transfer coefficients. Oral ingestion scenarios for liquid formulations are based on standard assumptions and formulae (Residential SOPs) which are designed to be screening level. Oral ingestion scenarios for hand-to-mouth exposures from granular formulations are based on a chemical-specific study designed to determine the residue and/or granules adhering to a wet hand after being repeatedly pressed onto turf treated with a granular formulation and are considered more refined. The risk estimates for children's residential exposures inclusive of a 3X hazard-based FQPA SF are considered adequately protective.

Environment and Human Health, Inc. (Dr. John Wargo):

<u>Comment</u>
Dr. Wargo recommends that atrazine be cancelled based on the following points. The burden of proof should be shifted to the registrants to show the absence of hormonal effects especially in early life. Millions of Americans are routinely exposed to atrazine without their knowledge or consent. EPA has no capacity to continue registration while preventing human exposure. The Agency has not demonstrated that there is a reasonable certainty of no harm to children from atrazine exposure. EPA is only now beginning a cumulative assessment to include other triazines found to have a common mechanism of toxicity. Why should the public bear the burden of water testing and filtraiton? The registrant should.

<u>HED Response</u>
The evidence that atrazine disrupts normal endocrine function is clear. Atrazine's documented neuroendocrine effects have become the main mechanism of toxicity, replacing the previous emphasis on carcinogenicity. Indeed, all of the toxic endpoints used in the atrazine human health risk assessment are based on this mechanism of toxicity. The registrant has devoted time and effort to researching the toxic mode of action in Sprague-Dawley rats leading to early onset of mammary adenomas and carcinomas. It has been suggested that the registrant conduct special studies to assess the endocrine effects of atrazine on early life and development.

Dr. Wargo comments that contamination and exposure to atrazine is widespread. HED agrees that atrazine is commonly found in water in USGS surveys and is relatively ubiquitous in streams, creeks, rivers, and lakes located in atrazine use areas. However, OPP does not base risk assessments on the kinds of data routinely collected by the USGS because it is not indicative of human exposure through drinking water. Although filtration typically used by community water systems (CWS) does not remove atrazine, raw water samples collected by USGS do not reflect treatment effects that do impact atrazine concentrations, i.e., activated carbon, nor do they reflect the effects of dilution and distribution systems at CWS. As mentioned, available drinking water monitoring data used in the risk assessment are limited, but are more reliable to estimate human exposures than available ambient water quality monitoring data.

HED also agrees with the comment that people are routinely exposed to atrazine without their consent and knowledge. However, this can be said of pesticides in general as they are detected in foods that we eat as seen through the USDA's Pesticide Data Program (PDP). In risk assessment, the key point is whether or not the levels of pesticides to which people are exposed result in hazardous impacts on their health. OPP's risk assessments are quantitative and are based on No Observed Adverse Effects Levels (NOAELs) of toxic endpoints modified by uncertainty/safety factors that are compared to estimates of exposures. OPP does not base its risk assessments on zero exposure as the comment seems to suggest it should.

HED's risk assessments for aggregate exposures of children to atrazine and its chlorinated degradates, as well as, hydroxy atrazine compounds indicate that although exposures through food are minimal (insignificant), exposures via certain lawn use products and in specific CWS are above levels of concern. That is, in general, OPP could not demonstrate reasonable certainty of no harm for certain lawn uses of atrazine products. However, the converse is suggested for drinking water exposures, i.e., in general OPP could demonstrate reasonable certainty of no harm for drinking water exposures except in specific CWS. Although the rigor of this finding is subject to limitations and uncertainties in the database, these residual concerns about uncertainty in the exposure database were taken into account in applying the 10X FQPA safety factor to the drinking water assessments.

However, for those specific CWS undergoing or preparing to undergo intensive monitoring, residual uncertainties regarding the extent and magnitude of exposure to chlorotriazines have been removed, therefore supporting a reduction in the FQPA safety factor to 3X. Based on the availability of reliable drinking water exposure data, HED has recalculated the DWLOC (drinking water level of concern) using a total risk assessment 300-fold uncertainty factor for those CWS currently undergoing or targeted for future intensive monitoring. For these CWS, the DWLOC for a 90-day average exposure becomes 37.5 ppb for total chlorotriazines. This value is based on an endpoint of 1.8 mg/kg/day, and a 300-fold uncertainty factor reflecting a 10-fold factor for interspecies variation, a 10-fold factor for intraspecies variability, and a 3-fold safety factor. The 3-fold safety factor reflects residual uncertainties associated with atrazine's toxic effects on the developing child only. For CWS without intensive monitoring as described above, the screening level DWLOC remains 12.5 ppb for total chlorotriazines.

In short, for those CWS with intensive monitoring, such that sufficient accuracy in the exposure assessments could be achieved, the portion of the FQPA safety factor reflecting residual uncertainties in the drinking water exposure database could be removed. Short of cancellation, OPP does have options to mitigate these specific residential uses that are of concern for children, and to mitigate impacts of atrazine on drinking water in general via rate reductions, and on CWS in specific via rate reductions, and local restrictions on use followed up by intensive monitoring.

As noted, the cumulative assessment for the triazines has not been completed. Aggregate risk assessments for simazine and propazine are required first.

<u>Comment</u>
Dr. Wargo brings up additional points regarding widespread atrazine contamination of water.

<u>HED Response</u>
Regarding atrazine's use, OPP is aware of the large volume of atrazine use in the US and the resultant impact of atrazine on the nation's water supplies. OPP recognizes that part of any mitigation proposal should emphasize reducing this environmental loading. HED is also aware that countries in Europe have banned atrazine because of widespread occurrence at greater than 0.1 ppb. These bans are not based however on risk assessments but are related to policies in those countries.

<u>Comment</u>
Dr. Wargo brings up additional points regarding atrazine's widespread contamination of water, averaging obscures peak concentrations, and degradates that are unregulated.

<u>HED Response</u>
HED agrees that the current monitoring scheme under the SDWA obscures peaks of atrazine that may be occurring seasonally. To address this issue, HED has based its drinking water risk assessment on intermediate-term exposures to 90-day average concentrations of atrazine and the chlorinated degradates rather than annual average concentrations. This assessment shows that seasonal peaks occur and are of greater concern for atrazine exposures than annual average exposures. HED defers to the Office of Water on the unregulated degradates comment.

<u>Comment</u>
Dr. Wargo brings up additional points regarding exposures to atrazine is in fog and rainwater.

<u>HED Response</u>
The comment expresses concern that the risk assessment did not include exposure to atrazine through fog and atmospheric deposition. Because HED used monitoring data for surface water to assess drinking water exposures, the contribution of atrazine to water supplies as deposited by atmospheric transport and rain is captured, i.e., is inherent in the database. There was no need to

estimate this contribution from drift with computer models, etc. Any contribution to the dietary exposure from rainwater is also reflected in the monitoring data used to assess dietary exposures. Based on the data available, dietary exposure estimates ranged up to 0.000017 mg/kg/day for food and up to 0.012 mg/kg/day for drinking water. The highest exposure estimates for food are approximately twice the maximum exposure estimate for air/fog concentrations of atrazine, and drinking water exposures are at least 3 orders of magnitude higher than food or air/fog exposures. Published literature indicates that atrazine has been detected and modeled in the atmosphere (air/fog) ranging from 10^{-9} up to 0.00001 mg/kg/day [3].

Although relative to drinking water and residential dermal exposures, exposures to atrazine through fog are expected to be minimal and not contribute significantly to risk, HED did consider inhalation of atrazine in its aggregate exposure assessments. These assessments consider inhalation exposure to the actual liquid and granular products containing atrazine as applied by the homeowner, which is expected to be in a much more concentrated form than atrazine dissolved in fog after being diffused and dissipated in the environment. HED estimates show that dermal exposures are greater than inhalation exposures for atrazine. Dermal exposures from use of atrazine products in and around the home are estimated to be 1.6 to 0.0034 mg/kg/day. Inhalation exposures for atrazine are estimated to be 0.00089 to 0.00001 mg/kg/day (1 to 5 orders of magnitude lower than dermal exposures). Published literature indicates that atrazine has been detected and modeled in the atmosphere (air/fog) ranging from 10^{-9} up to 0.00001 mg/kg/day [4]. The maximum exposure estimate is for locations within 200 km of the point of application. These estimated exposures are 5 to 9 orders of magnitude lower than the maximum estimated dermal exposures and at most equal to the lowest estimated inhalation exposures for homeowners handling concentrated liquid or granular atrazine products as well as several orders of magnitude less than drinking water exposures.

Therefore, HED expects inhalation exposure through fog to be insignificant relative to drinking water, dermal and inhalation exposures from handling liquid atrazine products, which have been included in the risk assessment. Given the conservative assumptions resulting in high-end estimates for the dermal and inhalation exposures used in the aggregate risk assessments, and the belief that exposure to atrazine through fog will be insignificant in comparison, HED believes any

[3] Cooter, EJ, and WT Hutzell, USEPA, National Exposure Research Laboratory,"A Regional Atmospheric Fate and Transport Model for Atrazine. 1. Development and Implementation", Environmental Science and Technology , Vol. 36, No. 19, 2002.

[4] Cooter, EJ, and WT Hutzell, USEPA, National Exposure Research Laboratory,"A Regional Atmospheric Fate and Transport Model for Atrazine. 1. Development and Implementation", Environmental Science and Technology , Vol. 36, No. 19, 2002.

potential exposures through fog have been adequately covered. Finally, HED believes that the 1000-fold uncertainty factor used for dietary exposure and the 300-fold uncertainty factor used for residential exposure used in conjunction with the conservative assumptions regarding residential exposure used in the atrazine human health risk assessment is adequately protective of aggregate exposures to atrazine.

Comment

Dr. Wargo brings up additional points regarding atrazine in breast milk and fetal exposure.

HED Response

Dr. Wargo expresses concern that atrazine may be transferred through breast milk and that this has not been considered in the risk assessment. However, HED points out that the human health risk assessment did consider both exposure and toxic effects associated with 1) the transfer of atrazine residues through milk via lactation, and 2) fetal exposures. The acute dietary risk assessment for food and drinking water is based on several developmental effects in offsrping and fetuses. One of these studies focused on the effects of exposure of the mother to atrazine on her suckling pups through lactation. This study showed prostatitis effects in the male pups exposed to atrazine through the mother's milk. The acute PAD is 0.01 mg/kg/day. This endpoint in conjunction with other developmental endpoints relevant to fetal effects formed the basis of the acute reference dose. The acute reference dose was determined through a weight-of-the-evidence analysis of three developmental studies and this fourth study on exposure through lactation. HED's intermediate-term and chronic risk assessments are based on an endpoint more than 5 times lower than the acute PAD or 0.0018 mg/kg/day. HED did not attempt to measure human breast milk for atrazine, but used instead used available information from animal feeding studies to estimate exposure. Since animals receive more atrazine in their diets than humans, this estimate of exposure through animal milk included in the dietary assessments should be conservative and protective of this type of exposure. HED therefore contends that not only exposure to atrazine through breast milk has been considered, but that relevant toxic endpoints regarding offspring and fetal effects have also been included in the human health risk assessments.

Comment

Dr. Wargo brings up additional points regarding the inadequacy of filtration to remove atrazine from drinking water, and environmental justice issues.

HED Response

Dr. Wargo states that conventional water treatment does not remove atrazine, but that atrazine must be removed by powdered activated carbon (PAC). This means the wealthier communities will treat while poor ones will not. HED agrees that conventional treatment will not remove atrazine and that PAC is required. As to the issue relating to the benefits of PAC only going to wealthier communities, HED must defer to the Office of Environmental Justice (OEJ).

Comment

Dr. Wargo expresses concern that the PLEX database is registrant generated and that the data are limited because too few samples are taken per year for a given community water system. This database will underestimate high seasonal exposures.

HED Response

HED agrees that there are limitations in the database used to estimate drinking water exposures. However, although the data in the PLEX database were complied by the registrant, these data were not generated by the registrant as the comment states. These data are in fact generated under the SDWA; they are compliance monitoring data. The registrant organized, collected, and compiled these data by going to the individual CWS operators. HED agrees that some CWS with monitoring data under the SDWA may have been missed out of PLEX contributing to uncertainties in the exposure database. HED agrees that sampling under the SDWA is too infrequent to capture short-term peaks, like seasonal pulses, of atrazine. Because of just these residual the uncertainties regarding the drinking water exposure database, along with residual uncertainties regarding developmental toxicity, HED determined that the full 10X FQPA safety factor should be applied to dietary risk assessments. As to increasing the frequency of compliance monitoring under the SDWA, HED must defer to OW on this issue.

Comment

Dr. Wargo brings up additional points regarding health effects at high doses including mammary tumors resulting from lifetime exposures.

HED Response

HED agrees that atrazine at high doses has been associated with a variety of health consequences in test animals, some but not all being relevant to humans. HED believes that the most important/dominant health consequences known to date have been reflected in the human health risk assessment.

Comment

Dr. Wargo states that the risk assessment document concludes that the atrazine toxicity database is complete, in spite of a lack of acute, sub chronic, and DNT studies.

HED Response

The HIARC document dated April 5, 2002 states that the toxicity database for atrazine is complete and adequate to evaluate potential adverse health consequences to infants and children under FQPA. Atrazine has one of the most extensive databases of any pesticide. The toxicity database is complete as per OPPTS Guideline requirements for atrazine. The DNT is not a guideline study, and the DNT is not appropriate to assess pituitary/endocrine function effects. For this reason, a DNT study has not been required. Similarly, acute and sub chronic neurotoxicity studies were not required for atrazine because the kinds of effects these studies test for (functional battery tests) are not expected for atrazine. Rather, the HIARC recommended special studies designed to examine atrazne's specific neuroendocrine mode of action as more useful.

Comment

Dr. Wargo expresses concerns regarding atrazine's effects on growth and development, and its potential as a carcinogen. He cites previously reviewed epidemiology studies and a case study in Louisiana at an atrazine manufacturing plant as evidence for continued concern regarding atrazine's carcinogenic potential. He notes the many alarming hormonal effects of atrazine, particularly for children.

HED Response

HED shares Dr. Wargo's concern for atrazine's effects on development and growth in the young. The risk assessment is based on toxic endpoints that are all related to either developmental or reproductive effects in keeping with atrazine's main mode of toxic action, i.e, neuroendocrine effects. Based on this concern, HED's HIARC and FQPA committees determined that a 10X safety factor for children was warranted based in part on residual uncertainties regarding atrazine's effects on growth and development along with uncertainties in the exposure database. On this point the HIARC concluded...

> *"Since the focus of the testing with Atrazine in the young rat has been limited to short periods of dosing to specific developmental periods, uncertainties are raised for susceptibility during earlier developmental periods as well as for consequences of earlier developmental exposure with longer duration of dosing throughout development. The effects of neurotransmitters/peptides (known to be critical for normal development and which could potentially translate into severe effects in children that may not be manifested until later in life) have not been fully characterized. And as the FIFRA Scientific Advisory Panel noted, there are concerns for behavioral effects in the young resulting from Atrazine's CNS mode of action and the dose level at which these effects might occur*

compared to reproductive/developmental effects[5]."

Therefore, HED believes its risk assessment, which incorporates this safety factor, is protective of children.

Epidemiological evidence linking atrazine to cancer does not show a direct causal effect. HED cannot quantitate a cancer risk in the absence of a toxic endpoint linking atrazine exposure directly to cancer. Since mammary tumors in the Sprague-Dawley rat have been the only tumors identified in association with atrazine exposure in test animals, and the toxic mechanism leading to these mammary tumors has been determined not to be operative in humans, HED has no toxic endpoint upon which to base a cancer assessment. However, the National Cancer Institute (NCI) is currently conducting a study on cancer and pesticide exposures among the agricultural community of which atrazine is a part. These data and additional information on the incidence of prostate cancer at a Louisiana atrazine production facility were requested and reviewed. This review indicates that it appears that most of the increase in prostate cancer incidence at the St. Gabriel plant is likely due to intensive prostate specific antigen (PSA) screening of employees conducted as part of the company's "Wellness Program." The study was insufficiently large and has limitations that prevent ruling out atrazine as a potential contributor to the increase observed. On balance, however, a role for atrazine seems unlikely because prostate cancer was found primarily in active employees who received intensive PSA screening; there was no increase in advanced tumors or mortality; and proximity to atrazine manufacturing did not appear to be correlated with risk.

Atrazine has also been tied to inflammation of the prostate in laboratory animals and changes in testosterone levels at high doses. However, neither condition has been tied to the increased risk of prostate cancer and the Agency concludes the animal data do not provide biologically plausible evidence to support atrazine as a cause of prostate cancer.

Other cancers besides prostate were found to have an elevated, though not statistically significant, increase in risk at the St. Gabriel plant. Other studies have suggested an increased risk for ovarian, breast, and other cancers, including non-Hodgkin's lymphoma. However, these

[5]SAP Report No. 2000-05; Atrazine: Hazard and Dose Response Assessment and Characterization. "Because of the rapid developmental brain changes...the influence of Atrazine on neurotransmitters in the hypothalamus and on GnRH may well have a differential, permanent effect on children. This phenomenon is the basis of the relatively new field of behavioral teratology. Atrazine could influence the migration of cells and the connectivity of the CNS. The influence of Atrazine on the hypothalamus and on GnRH may have a differential effect on children. This effect could be latent, and emerge later during the challenge of puberty, or during senescence. Behavioral alterations may be the most sensitive outcome. This possibility should be addressed...."

studies are at best preliminary and should not serve as a basis for implicating atrazine as a human carcinogen due to their methodological limitations. See the IRED for further discussion.

Comment

Dr. Wargo brings up the triazine common mechanism decision and the chemical mixture issue as a potential problem for atrazine as USGS studies have found that it co-occurs with other pesticides.

HED Response

HED expects to begin work on the triazine cumulative risk assessment after completing work on the aggregate simazine and aggregate propazine risk assessments. Until these single chemical risk assessments are completed, HED cannot comment on the outcome of the cumulative risk assessment for the triazine common mechanism group. As to the chemical mixtures issue, HED acknowledges that pesticides co-occur, but OPP has no statutory authority to regulate or methodology to assess risks associated with chemical mixtures not based on a common mechanism of toxicity.

Beyond Pesticides/NCAMP:

Comment

NCAMP expresses concern that atrazine is widespread in water supplies and is a powerful endocrine disruptor. It cites several examples of endocrine effects in wildlife and test animals. They express concern for mammary tumors in rats exposed to atrazine and cite epidemiological studies' results to bolster this concern including the prostate cancer study at the St. Gabriel facility. NCAMP also provides mitigation measures for atrazine including: strengthening and enforcing the drinking water standard, banning all residential uses, and switching to widely available alternatives.

HED Response

HED agrees with NCAMP that atrazine is an endocrine disruptor. The human health risk assessment has been based entirely on developmental and reproductive effects believed to be driven by a neuroendocrine mode of action believed to common to atrazine, its chlorinated degradates, and simazine and propazine. However, HED must defer to the EFED for a response on the specific wildlife effects noted.

The mammary tumors in the female Sprague-Dawley rat have been attributed to atrazine's ability to affect the neuroendocrine system in the rat. However, the actual mechanism by which tumor formation occurs was determined by a June 2000 SAP to be "unlikely to be operative in humans". Although the tumor formation in the rat and consequently the cancer endpoint are no longer considered relevant to human health, atrazine's ability to alter hypothalamic/pituitary function in test animals is considered to be relevant to humans, and consequently, the entire human health risk assessment was based on toxic endpoints reflecting a neuroendocrine mode of action.

As to the epidemiological evidence for cancer in humans, the available epidemiologic data on atrazine do not make a direct causal link between atrazine and cancer. See the response to Dr. Wargo on the cancer issue on p. 51 and the IRED for further discussion.

By way of history, OPP has reviewed the many epidemiological studies on atrazine cited by NCAMP. These studies deal with various cancers of the ovary, prostate, colon, breast, leukemia, non-Hodgkin's lymphoma. The results of these reviews can be found in their entirety in the following memoranda: "Review of Atrazine Incident Reports", DP Barcode: D270014, "Review of five epidemiological published articles for SAP", DP Barcode: D262405, and "A Follow-up Study of Mortality Among Workers at the Novartis St. Gabriel Plant & Follow-up Study of Cancer Incidence Among Workers in Triazine-Related Operations at the St. Gabriel Plant, DP Barcode: D281568 & D278933. The studies reviewed are: IARC Overall Evaluation of Carcinogenicity to Humans, "A Follow-up Study of Workers at the Ciba-Geigy St. Gabriel Plant", E. Delzell, et al, April 8, 1996, "Atrazine, An Epidemiological Study at the Schweizerhalle Plant", R. Gass et al., January 15, 1993, Ciba Geigy Herbicide Mortality Study, "Ovarian Mesothelial Tumors and Herbicides: A Case-Control Study", Donna, et al., 1984, "Triazine Herbicides and Ovarian Epithelial Neoplasms, Donna, et al., 1989, "Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma", Hoar, et al., 1986, "Pesticide Exposures and Other Agricultural Risk Factors for Leukemia Among Men in Iowa and Minnesota", Brown, et al., 1990, "Herbicides and Colon Cancer, Hoar, et al., 1985, "A Case-Control Study of Non-Hodgkin's Lymphoma and Agricultural Factors in Eastern Nebraska, Zahm, et al., 1988, "Farming and Non-Hodgkin's Lymphoma, Cantor, et al., 1985, "Role of the Herbicide Atrazine in the Development of Non-Hodgkin's Lymphoma ", Zahm, et al., 1993, "Triazine Herbicide Exposure and Breast Cancer Incidence: An Ecological Study of Kentucky Counties", Kettles, et al., 1997, and "Correlation Analysis of Pesticide use Data and Cancer Incidence Rates in California Counties", Mills, et al., 1998.

In summary, reviews of the epidemiological studies dealing with prostate cancers and exposure to atrazine conclude that the increases in prostate cancers among workers manufacturing atrazine are attributable to the increased PSA screening conducted at the plants as a part of routine check-ups at the plants, and could not be conclusively linked to atrazine exposure. The reviews of studies dealing with non-Hodgkin's lymphoma (NHL) concluded that there was little to no increase in the risk of NHL attributable to the agricultural use of atrazine after adjustment for the use of other pesticides, specifically 2,4-D and organophosphates. Or put another way, there is little evidence that atrazine exposure explains any appreciable increase in NHL over the last 15 years in the US. Reviews of studies dealing with ovarian cancers conclude that definite exposure to triazines was associated with a 2 to 3-fold increase of borderline significance in the risk for ovarian cancer, but that confirmatory studies were needed as this study was small and potentially confounded by exposure to other herbicides, which was not controlled for in this study. Reviews of studies for leukemia conclude that the results for an association between leukemia and atrazine are unremarkable. Reviews of studies on breast cancers show only modest increases in risk that are in the same range as non-chemical risk factors not measured. The reviews conclude that in general, epidemiological studies containing information on atrazine exposures and cancer either indicate no significant increases in cancer risk that is directly associated with atrazine exposure, or raise more questions than they answer.

OPP concludes that "the results of the human epidemiology studies do not provide clear evidence of an association between triazines and cancer. Some of the studies, particularly those in which hormone-responsive cancers such as breast, ovary and prostate, were examined, are suggestive of a possible association. There is also suggestive evidence of a possible association of triazine exposure and NHL. Further epidemiologic research is needed - especially in the area of hormone-responsive cancers" (Final Report - Atrazine: Hazard and Dose-Response Assessment and Characterization, Part B- Hazard Assessment and Review of Available Studies, report prepared for June 2000 SAP or www.epa.gov/scipoly/sap/2000/index.htm#June 27).

Regarding strengthening and enforcing the atrazine drinking water standard in general, HED must defer to the OW. However, HED recognizes that atrazine is widespread in the Midwest. The majority of community water systems (CWS) with risk estimates exceeding levels of concern are located in the Midwest. As to the CWS identified in the OPP human health risk assessment, mitigation to reduce the impacts of atrazine on those CWS is currently being discussed and will be negotiated with the registrant as part of a reregistration eligibility decision.
HED agrees that residential uses of atrazine show risk estimates of concern for children, particularly for children playing on lawns shortly after application of liquid products. Mitigation for those uses and exposure patterns will be discussed as a part of the reregistration eligibility decision.

HED must defer to the BEAD regarding the availability of atrazine alternatives.

People for the Ethical Treatment of Animals (PETA):

Comment

PETA, believing the current MCL for atrazine is based on the rat study in which mammary female tumors in Sprague-Dawley rats were noted, states that the mode of action behind the formation of these tumors is "not relevant to humans because there are considerable differences between the hypothalmic-pituitary ovarian functions in humans and rats". Given this finding, they question how EPA can go forward with animal testing under the endocrine disruptor screening program if it has been decided that these tests don't apply to humans.

HED Response

PETA correctly notes that the tumors associated with the Sprague-Dawley rat are based on a specific toxic mechanism "not likely to be operative in humans" (June 2000 SAP report). However, the same SAP noted that although the mechanism resulting in mammary tumor formation in the Sprague-Dawley rat is not relevant to humans, the potential for atrazine to alter the function of the hypothalamus/pituitary in a generic neuroendocrine mode of action is. To complete the SAP's thoughts on the subject, the following is an excerpt from the human health risk assessment for atrazine,

> *"Atrazine alters hypothalamic gonadotrophin releasing hormone (GnRH) release in rats. There are also some data that indicate that atrazine diminishes norepinephrine in the rat hypothalamus as an initial or early site of action which in turn leads to diminished GnRH release. Atrazine also increases dopamine levels which can result in a diminished pituitary secretion of prolactin. Therefore, atrazine appears to operate at the level of the hypothalamus. In both humans and rats, hypothalamic GnRH controls pituitary hormone secretion (e.g., luteinizing hormone (LH), and prolactin (PRL). The hypothalamic-pituitary axis is involved in the development of the reproductive system, and its maintenance and functioning in adulthood. Additionally, reproductive hormones modulate the function of numerous other metabolic processes (i.e., bone formation, and immune, central nervous system (CNS) and cardiovascular functions). Therefore, altered hypothalamic-pituitary function can potentially broadly affect an individual's functional status and lead to a variety of health consequences.*
>
> *The report of the Scientific Advisory Panel (SAP) convened in June 2000 to consider these health consequences of exposure to atrazine, indicated that "..it is not unreasonable to expect that atrazine might cause adverse effects on hypothalamic-pituitary function in humans." Therefore, atrazine's effect on ovarian cycling and the pre-ovulatory LH surge (as well as its effects on pregnancy, puberty, suckling induced PRL release which leads to*

prostatitis) are viewed as neuroendocrinopathies or biomarkers indicative of atrazine's ability to alter hypothalamic-pituitary function in general. It should be noted that atrazine's neuroendocrine effects have been demonstrated in several strains of rats (SD, Long Evans, and Wistar)."

Therefore, PETA incorrectly interpreted the SAP report on atrazine in assuming that endocrine testing results will not be extrapolated to humans. In fact, the opposite is the case; the SAP viewed the endocrine effects in the rats as indicative of potential endocrine effects in humans. Consequently, the entire human health risk assessment for atrazine is based on developmental and reproductive endpoints seen in test animals believed to be associated with the neuroendocrine effects of atrazine.

As to the use of human dermal absorption data in the risk assessment, the revised risk assessment used a 6% dermal absorption factor based on human data. The revised preliminary risk assessment used the animal data modified by the human data.

<u>California Department of Pesticide Regulation (CDPR):</u>

<u>Comment</u>

California Department of Pesticide Regulation (CDPR) comments that up-regulation of aromatase may be the mechanism involved in sub chronic/chronic effects seen in rat studies and used in the risk assessment. They cite endocrine effects in amphibian species in support of this hypothesis. They also state that sex organ effects are extremely sensitive to reduced food intake and as such, in the Wistar and SD rat, reduced organ weight, delayed preputial separation and delayed puberty cannot be considered direct effects of atrazine dosing. Their value for risk assessment must therefore be considered dubious. They cite a study involving exposure of male SD rats during postnatal days 22-47, in which the average body weight of the rats at 100 mg/kg/day was reduced by about 9%. The authors also pair-fed a group and found that even mild food restriction resulted in reductions in serum testosterone concentration, weights of androgen-dependent organs, and serum LH concentration; the same deficits that were seen in atrazine rats. They concluded that the effects of atrazine on male reproductive tract in rats receiving greater than 50 mg/kg/day could not be distinguished from the effects of reduced food consumption. The dose levels in this study were 1, 2.5, 5, 10, 25, 50, 100, and 200 mg/kg/day.

<u>HED Response</u>

Regarding aromatase, HED's response on page 17 is reiterated below.

The SAP was asked to comment on whether alternative modes of action (re: mammary tumors) have been sufficiently discussed and ruled out by the Agency. The SAP stated "There are no data that would suggest other plausible modes of action. The increased level of hormones and the increased level of hormones alone, can account for the increased incidence of mammary tumors in Sprague Dawley female rats. The proposed mode of action is plausible and each step in the pathway has been shown to be affected in atrazine treated rats. None of the effects are based on speculation.

Previously, OPP concluded that it is plausible that **enhanced** aromatase activity may have some influence on the development of mammary tumors in SD female rats. However, whether or not enhanced aromatase activity is a significant contribution to the carcinogenicity, or other effects, of atrazine remains to be determined. EPA acknowledged the fact that an increase in aromatase activity would be consistent with dose-response increases in estradiol and estrone and decreases in testicular testosterone noted in a study that examined the effects of atrazine on pubertal development. The doses that resulted in effects on these hormones were well above doses that led to reproductive/developmental effects. Additionally, it was acknowledged that it is plausible that enhanced aromatase activity may have some influence on the development of mammary tumors in SD female rats; however, there are no data to date on whether enhanced aromatase activity significantly contributes to the carcinogenicity observed. The effect of the chlorotriazines on aromatase remains an active research issue, in general.

The EPA's National Health and Environmental Research Laboratory (Dr. Ralph Cooper's laboratory) have recently evaluated the effects of atrazine and DACT on aromatase activity in the rat. Preliminary results show that DACT does not effect aromatase activity and atrazine actually causes a **decrease** in aromatase, but only at high doses. Based on the weight of evidence, enhancing aromatase activity does not appear to be a mode of carcinogenic action, particularly given the recent findings of Ralph Cooper. Further, if this were a primary mode of action, a more consistent finding of tumors at estrogen sensitive sites would be anticipated in the rodent carcinogenicity studies. Lastly, the June 2000 FIFRA Scientific Advisory Panel was specifically asked about OPP's assessment of other possible other modes of carcinogenic action, and the SAP agreed that there is an insufficient basis to link effects on aromatase to the mammary gland tumor response in female Sprague Dawley rats.

With regard to research data relating to the effects of atrazine on amphibians, EPA has not yet reached conclusions on these data, and therefore does not have any specific comment on these research efforts. EPA is planning to convene an independent scientific peer review [the FIFRA Science Advisory Panel (SAP)] of information related to potential effects of atrazine on amphibians sometime in mid- 2003.

Although atrazine and food restriction produce many of the same effects, they may do so by different mechanisms. The study cited by DPR did not show any effects at dose levels that did not affect bodyweight; however, the study used in the short-term risk assessment did show effects at dose levels not affecting body weight. In the cited study by DPR, restricted food consumption was observed at dose levels greater than 50 mg/kg/day, and the effects on testosterone concentration, weights of androgen- dependent organs, and serum LH concentration were observed only at the high-dose levels > 50 [at 100 and 200 mg/kg/day]. There were no apparent effects on these parameters at dose levels where body-weight effects were not observed, which supports DPR's concern.

However, in the Stoker study [pubertal study in males used for short-term risk assessment], delayed preputial separation was observed at 12.5 mg/kg/day and above, ventral prostate weight was decreased at 50 mg/kg/day or greater, but body weights were decreased mainly at the 200 mg/kg/day dose level and in the pair-fed control group. In this latter study, the delay in preputial separation and decreased ventral prostate weight were observed in the absence of any effect on body weight. In the pubertal assay [used for short-term risk assessment], the NOAEL is 6.25; LOAEL is 12.5 mg/kg/day. Body weights on post-natal-day (PND) 23 [start of dosing] at 12.5 mg/kg/day were 96% of control and 98% of control on the day of preputial separation [PPS]; 92% on PND 43 and 95% on PND 53. Dose levels tested in this study were 6.25, 12.5, 25, 50, 100, 150, 200, and a pair-fed group. At 50 mg/kg/day, body weight was greater than control on PND 23 and at PPS; 98% of control at all other times. At 100 mg/kg/day, 99% at PPS and 90% on PND 43, etc. There were changes [delays] in PPS in atrazine groups that did not affect body weight and more severe delays in the high-dose group that did display decreased body weight. Ventral prostate weight was decreased compared to the vehicle control at 50 mg/kg/day and greater, as was the pair-fed group ; also an effect at a dose level not affecting body weight.

One member on the June 2000 SAP for atrazine felt strongly that the appetite suppressant properties of atrazine are what induces the neuroendocrine alterations seen following atrazine exposure. The easiest way to examine appetite suppression is simply to look at food consumption, which Cooper et al. did in the pubertal assays. If atrazine is an appetite suppressant then, clearly, atrazine exposed animals will show decreased food consumption.

One thing that becomes evident from examining food consumption in the studies from the atrazine database is that if atrazine causes appetite suppression, it does so only at higher doses (above 20 mg/kg/day) and even then the appetite suppression is, at worst, mild. Dr. Cooper did see some mild suppression at high doses but nothing at lower doses causing effects. Food consumption data illustrating this point from 6 studies (the 28 and 6 month LH surge studies, three 2-year bioassays and one 1-year bioassay) and their references are shown below:

The greatest decrease in food consumption seen in this set of 6 studies was at the 29.44 mg/kg/day group of the 28 day study. In this group of this study there was a 21% decrease in food consumption during week one. Other than this dose, at this time point in this study, no decrease in food consumption was greater than 8% compared to controls.

28 day LH surge study; MRID 43934406; TXR 013996

Food consumption. Values shown are in grams.

	Control	2.5	5.0	40	200
Week 1	$\bar{x}$= 129 SD= 15.8	$\bar{x}$= 128 SD= 15.1	$\bar{x}$= 129 SD= 12.7	**$\bar{x}$= 124*** SD= 13.2	**$\bar{x}$= 102*** SD= 12.4
Week 5	$\bar{x}$= 143 SD= 15.7	$\bar{x}$= 140 SD= 19.2	$\bar{x}$= 141 SD= 18	$\bar{x}$= 141 SD= 15.3	**$\bar{x}$= 133*** SD= 15.7
Weeks 1-5	$\bar{x}$= 671 SD= 62.7	$\bar{x}$= 667 SD= 66.6	$\bar{x}$= 675 SD= 58.8	$\bar{x}$= 667 SD= 59	**$\bar{x}$= 620*** SD= 60.2

* $p \leq 0.05$ compared to control.

In this study there is little effect of atrazine on food consumption at 40 mg/kg/day where LH surge suppression was noted. Food consumption between control and 40 mg/kg/day at 5 weeks and for the entire study differ by less than 1.5%. At week one there is a statistically significant difference between the two groups, however the percent difference is still only 3.9%.

6-month LH surge study; MRID 44152102;

Food consumption. Values shown are in grams.

	Week 1	Week 13	Week 25	Weeks 1-25
Control	$\bar{x}$=124 SD=17.4	$\bar{x}$=138 SD=14.4	$\bar{x}$=137 SD=16	$\bar{x}$=3438 SD=255.1
1.8 mg/kg	**$\bar{x}$=131*** SD=16.6	$\bar{x}$=141 SD=14.8	$\bar{x}$=143 SD=16.1	$\bar{x}$=3462 SD=259.6
3.65 mg/kg	$\bar{x}$=127 SD=16.7	**$\bar{x}$=131*** SD=15.6	$\bar{x}$=135 SD=19	$\bar{x}$=3455 SD=302.9
29.44	**$\bar{x}$=114***	**$\bar{x}$=127***	$\bar{x}$=135	**$\bar{x}$=3309***

mg/kg	SD=11.1	SD=12	SD=14.9	SD=293.7

* p$\leq$ 0.05 compared to control

At week 13 food consumption is statistically significantly decreased compared to controls, but this decrease is only 5%. For the entire study food consumption is similar between control and 3.65 mg/kg/day and is, in fact, a tiny bit greater at 3.65 compared to control.

In both 28 day and 6-month LH surge LH surge and estrous cycles are altered at atrazine doses which affect food consumption little or not at all.

Thakur terminal sacrifice study with SD; MRID 42204401

Food consumption. Values shown are in grams.

	Control	3.79	23.01
Weeks 1-24	$\bar{x}$= 2610.9 SD=196	$\bar{x}$= 2637.5 SD= 240.8	$\bar{x}$= 2544 (-2.5%) SD= 181.9
Weeks 1-52	$\bar{x}$= 3659.7 SD= 287.3	$\bar{x}$= 3661.7 SD= 275.9	$\bar{x}$= 3573.1 (-2.4%) SD= 242.5
Weeks 1-104	$\bar{x}$= 5725 SD=398.6	$\bar{x}$= 5632.6 SD= 355.5	$\bar{x}$= 5662.1 (-1.1%) SD= 335.5

* p$\leq$ 0.05 compared to control.

Morseth 2 year study intact vs OVX; MRID 44544701

Food consumption. Values shown are in grams. Food consumption measured weekly from weeks 1-13 and every 4th week thereafter

	Control	1.5	3.1	4.2	24.4
Weeks 1-21	$\bar{x}$= 2049	$\bar{x}$= 1988	$\bar{x}$= 2095	$\bar{x}$= 2071	$\bar{x}$= 1939 (-5.4%)
Weeks 1-52	$\bar{x}$= 3145	$\bar{x}$= 3153	$\bar{x}$= 3266	$\bar{x}$= 3252	$\bar{x}$= 3078 (-2.1%)
Weeks 1-104	$\bar{x}$= 4874 SD= 266.3	$\bar{x}$= 5075 SD= 359.5	$\bar{x}$= 5118 SD= 499.2	$\bar{x}$= 5213 SD= 383.6	$\bar{x}$= 4830 SD= 343.5

(-1.0%)

The food consumption data from the pair of 2-year bioassays shown above shows little indication of an appetite suppressant effect. The food consumption is decreased most at doses above 20 mg/kg/day at the early timepoints. Even then the decrease is only 5% at most (compared to controls). Early onset of mammary tumors, particularly carcinomas was evident in both these studies at 3.79 and 4.2 mg/kg/day - doses at which food consumption was similar to control values (and in fact was slightly increased compared to controls).

Female daily mean food consumption from Mayhew (MRID 00141874). Values shown are in grams.

	Control	0.5 mg/kg/day	3.5 mg/kg/day	25 mg/kg/day	50 mg/kg/day
Week 1	17.5	17.8	17.9	16.1**	14.4**
Week 26	19.7	19.3	19.6	19.1	18.4*
Week 52	20.7	20.5	20	20	19.8
Week 104	18.1	17.4	17.3	18.1	16.5

* p < 0.05
** p < 0.01

One year study; MRID 43934402

Mean weekly food consumption. Values shown are in grams.

	Week 1	Week 26	Week 50
Control	$\bar{x}$= 16.34	$\bar{x}$= 17.23	$\bar{x}$= 19.42
0.8	$\bar{x}$= 16.66	$\bar{x}$= 17.3	$\bar{x}$= 18.68
1.7	$\bar{x}$= 16.25	$\bar{x}$= 17.0	$\bar{x}$= 19.18
2.8	$\bar{x}$= 16.27	$\bar{x}$= 16.89	$\bar{x}$= 18.12
4.1	$\bar{x}$= 16.71	$\bar{x}$= 16.83	$\bar{x}$= 19.52
23.9	$\bar{x}$= 15.8	$\bar{x}$= 17.04	$\bar{x}$= 18.55

The data from these two studies again shows that decreased food consumption occurred at above 20 mg/kg/day and the decreases were most severe at the early timepoints.

In conclusion, one member of the SAP (Dr. Phil Landfield) has advanced an hypothesis that atrazine's appetite suppressant properties are what induces the neuroendocrine alterations leading to mammary tumors. This hypothesis first assumes that atrazine actually has appetite suppressant properties, and second, assumes that these properties induce the neuroendocrine alterations.

However, there is not strong evidence that atrazine has any appetite suppressant properties at all. Food consumption is decreased if the doses are high enough (above 20 mg/kg/day), but it is rarely decreased by more than 10%. Even then, the effect is seen only in the first few weeks of dosing. The atrazine database provides ample evidence of neuroendocrine alterations (and tumor development) occurring at doses below 20 mg/kg/day.